OXFORD MEDICAL OUTLINE SERIES

HISTOLOGY AND EMBRYOLOGY

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PREFACE

THIS OUTLINE presents in condensed form the most important facts concerning the structure and development of the organs of the human body. Following the trend in American textbooks of Histology, the microscopic anatomy of the central nervous system is not included; it will be found in the outline of Neuro-Anatomy of this series. At the risk of putting undue emphasis on structure it was deemed advisable to omit those functional interpretations which are still the subject of controversy; in some instances, however, the different points of view are briefly mentioned.

Several textbooks have been consulted during the preparation of this outline, and the subject matter so arranged as to conform broadly with those in common use. Its value will be increased if the student furnishes his own illustrations copied from actual preparations, for which adequate space has been provided. It must be remembered, nevertheless, that the outline is not intended as a laboratory guide but merely as a supplement to a textbook.

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HISTOLOGY

Histology deals with the cell associations or tissues which, variously combined, form the body of plants and animals. It is actually the complement of gross anatomy and an indispensable preliminary for the understanding of physiology and pathology.

PART ONE: THE CELL

Cells can be studied in the living condition or after they have been killed with reagents and stained. Because of the difficulties encountered in the study of most vertebrate living cells the second procedure is the one generally followed in mammalian histology.

I. Structure

Most animal cells consist of a mass of cytoplasm enclosing a nucleus. Binucleate cells and cells with several nuclei may occur normally in mammals.

A. Cytoplasm. In fixed cells the cytoplasm appears as a slightly granular substance. This, however, is the result of coagulation. In the living condition it is supposed to be an aqueous colloidal solution of proteins, fats, carbohydrates and inorganic salts. It is bounded externally by a very thin membrane. Besides the nucleus, cytocentrum and organoids the cytoplasm may have inclusions which vary within the same cell at various times and differ in diverse cells.

1. **Proteins.** Usually appear in granular form.
2. **Carbohydrates.** Occur chiefly as granules of glycogen, regarded by some as due to precipitation.
3. **Fats and lipoids.** Fat can be seen as droplets of various sizes in living cells; in fixed and stained sections it has usually been dissolved, leaving empty spaces (vacuoles).
    a. It can be stained with certain dyes (Sudan III, scarlet red).
4. **Pigment.** Occurs in many cells. It may be yellowish and rather soluble (lipochrome) or black (melanin). The latter is very resistant to the action of reagents.

a. Some cells contain pigment throughout life and are called chromatophores (or melanophores if they have melanin).

5. **Crystals and crystaloids.** They are known to occur in some mammalian cells, but their presence is by no means constant.

a. Their chemical nature and function are unknown.

B. Nucleus. The nucleus is usually a spherical vesicle enclosed within a membrane and containing diverse substances which differ in appearance in stained cells.

1. **Nuclear sap,** a fluid ground substance which fills the nucleus.
2. **Linin threads.** They usually form a delicate meshwork which occupies the whole nucleus. Linin does not stain.
3. **Chromatin.** Appears as granules of various sizes scattered along the linin meshwork or congregated at the point of intersection of the mesh, where they form irregular knots. Chromatin stains deeply with basic dyes.

a. Its distribution within the nucleus is sometimes a valuable diagnostic feature.

4. **Nucleolus.** This is a spherical mass of acidophil substance floating in the nuclear sap or attached to the linin meshwork. More than one may be present.

C. Cytocentrum (cell center). In practically every cell there is a condensed portion of cytoplasm, termed the cytocentrum. In most mammalian cells it occurs near the nucleus.

1. It contains a small sphere (centrosome) which in turn has two or more granules or rods, the centrioles.
2. It plays an important part during mitotic division.

D. Organoids. They are structures found in all cells, comparable with the organs of the multicellular organism.

1. **Golgi network (reticular apparatus).** It consists typically of a variable number of anastomosed strands which can be impregnated with osmic acid and also with silver.

a. The network may occupy a restricted area of the cell or be more scattered, and in some instances the strands are independent from each other ('dispersed state').

b. It has been regarded by some as an organoid concerned with secretory phenomena of the cell.

2. **Mitochondria.** Granular or rod-like structures which stain supravitally with Janus green. Their numbers vary considerably;

they divide and when they appear as granules they can arrange themselves into filaments.

a. They have also been supposed to be concerned with secretion.

3. Fibrils. Fibrils are observed in certain cells, and they have been regarded by some as some sort of intracellular skeleton. This may be true in the case of the tonofibrils present in epithelial cells; in other cells, however, their function is probably more specific (neurofibrils of the nerve cell; myofibrils of the muscle fibers).

II. Reproduction

Cells have the properties of all living matter, namely, metabolism, irritability, contractility and reproduction. The study of the first three falls within the domain of general physiology. The phenomena of reproduction, on the other hand, are of direct interest to the histologist because they can be recognized in sections of tissues. Cell reproduction takes place through a process of division.

A. Amitotic (direct) division. This is of rare occurrence and is thought to lead to degeneration of the cells. The nucleus elongates, constricts in the middle and finally separates into halves. Fission of the cytoplasm takes place soon afterwards.

B. Mitotic (indirect) division.

1. Somatic mitosis. Takes place in all cells of the body. Four periods are recognizable: prophase, metaphase, anaphase and telophase.

a. Prophase. The most characteristic feature is the transformation of the chromatin-linin reticulum into more or less elongated bodies (chromosomes) the number of which is characteristic for a given species (48 in man).

(1) Simultaneously with the nuclear changes the centrioles—usually surrounded by fine radiating filaments (astral filaments)—move away from each other and place themselves in opposite poles of the nucleus.

(2) Toward the end of the prophase the nuclear membrane is dissolved, releasing the chromosomes which become attached to some of the astral filaments; the threads attached to the chromosomes are now called spindle fibers.

b. Metaphase. The chromosomes arrange themselves into a plate at right angles to the axis determined by the centrioles (equatorial plate).

(1) Each chromosome splits lengthwise (if not already split during the prophase).

(2) The spindle is now fully constituted.

c. Anaphase. The astral fibers attached to the chromosomes seem to contract, pulling the halves of each chromosome toward the poles of the spindle.

(1) As a result of the longitudinal splitting of the chromosomes each daughter cell will receive the same number (48 in man).

d. Telophase. This is the final stage of the process during which the daughter groups of chromosomes (now in the poles of the spindle) gradually fade from view as they elongate and lose their compact appearance.

(1) A nuclear membrane appears around each group.

(2) Division of the cytoplasm takes place at this moment or earlier, in the anaphase.

2. Maturation mitosis. This occurs in the course of the formation of the germ cells in the two sexes. It differs from the somatic in that it separates whole (homologous) chromosomes previously paired during synapsis (see pp. 77, 83).

3. Abnormal mitoses. Irregularities in the process of mitosis are by no means rare, particularly during the formation of the male germ cells. They usually lead to death of the cell.

a. Multipolar mitoses, i.e. mitoses in which several spindles are formed, are found in pathological growths such as cancer and tumors.

III. Degeneration and Death

Cells die in various numbers during the life of the individual without affecting his health. Widespread cell death caused by alterations of metabolism, poisons and bacterial toxins, prolonged anaemia due to thrombosis (infarction), inflammation, hemorrhage, etc., falls within the domain of pathology. Death due to senility of the cells or to physiological changes must be taken into account in histology because degenerating or dead cells can be found in sections of almost any organ.

A. Senility. The life span of the cells of the body varies greatly. Some elements as the red blood corpuscles and leucocytes are short-lived and perish daily in large numbers; others seem to live for

many months or years. Degenerative changes are manifested in various ways:

1. **Nuclear changes.** The chromatin contracts into a dense mass (pyknosis), or breaks up into irregular, deeply stained masses (karyorhexis) or is gradually dissolved in the cytoplasm (karyolysis). These changes, however, normally take place during the formation of red blood corpuscles, which is not a degenerative process.

2. **Cytoplasmic changes.** The cytoplasm of degenerating cells may become homogeneous or glassy, or the whole cell changed into colloid, or the cytoplasm may develop large vacuoles, or else it may shrink and stain more deeply.

   a. The changes mentioned above also occur when cells degenerate under the influence of pathological agents; they are also seen in cells that have been phagocytosed.

B. Physiological degeneration. Some cells are doomed as the result of the production of substances which, however, play a protective rôle for the organism.

1. The production of keratin in the cells of the superficial layers of the skin and of fat in the cells of the sebaceous glands may be mentioned as examples.

C. Physiological atrophy. This term is applied to the decrease in size which occurs normally in the cells of certain organs; it may be also caused by old age.

1. **Involution atrophy.** This occurs in organs which undergo regression after a period of physiological activity (thymus, corpus luteum of ovary).

2. **Senile atrophy.** Observed in many organs of subjects of advanced age. The cells become progressively smaller while retaining their normal characteristics.

3. **Fat cell atrophy.** Seen in lean but otherwise normal individuals. Cells undergoing atrophy closely resemble early stages of fat deposition in the fetus.

D. Desquamation. The cells drop out of alignment and are lost (skin, mucosa of mouth, oesophagus, bladder, etc.).

E. Postmortem changes. They are seen in organs fixed some time after death, especially in material collected at the autopsy room. The changes observed are to be distinguished from those mentioned above.

PART TWO: THE TISSUES

The association or grouping of cells which have the same origin and perform similar functions is called a tissue. The tissues of the mammalian body are: I. Epithelium; II. Blood and lymph; III. The supporting tissues (connective tissue; reticulo-endothelium; cartilage; bone); IV. Muscular tissue; V. Nervous tissue.

EPITHELIUM

In epithelium the cells are cemented together by a small amount of intercellular substance; they are of uniform type or differ in shape and function. Epithelium is usually separated from the underlying tissue by a basement membrane. It lacks vessels of its own.

The three blastodermic layers of the embryo give rise to epithelium. Some varieties cover the surface of the body and line closed cavities, or cavities which communicate with the outside (covering epithelium). Others consist of secretory cells arranged in various ways (glandular epithelium). Finally, the epithelial cells may receive stimuli which are taken up by sensory nerve endings (neuroepithelium).

I. Covering Epithelium

The cells form a single layer or they are arranged into several layers. Transitions also occur.

A. Single-layered epithelia:

1. **Squamous or pavement epithelium.** Flattened cells with irregular or wavy outlines. Nucleus flat, oval or round in outline.
   - **a. Endothelium.** Lines the cavities of the heart and the lumina of the blood and lymph vessels.
   - **b. Mesothelium.** Similar to the preceding except that it lines the serous (closed) cavities of the body (pericardium, pleura and abdominal cavity).
2. **Cuboidal.** In vertical section the cells appear as squares; on surface view they have polygonal shape due to mutual pressure.
3. **Columnar or prismatic.** The cells are tall prisms due to mutual pressure but in a vertical section appear as rectangles. The basal end of the cell—in contact with the basement membrane—is often pointed or even branched (intestine).

4. **Ciliated.** The cells bear cilia on their free surfaces. The cilia are either motile (bronchi, oviduct) or non-motile, resembling a brush border.

B. Stratified (many-layered) epithelium. The shape of the cells varies in the different layers, which are produced through mitoses of the cells resting on the basement membrane (basal layer). The most superficial cells are, therefore, the oldest.

1. **Stratified squamous.** The cells on the surface are flat; below they gradually change into irregular polyhedral cells. The basal layer is formed of cuboidal or low columnar cells.
   a. **Production of keratin (cornification)** results in the disappearance of the nuclei of the superficial cells (skin).
   b. **In the absence of cornification** the superficial cells retain their nuclei and are not so flat (mouth cavity, oesophagus, cornea, vagina, etc.).
2. **Stratified columnar.** The superficial cells are columnar but fail to reach the basement membrane (cavernous urethra).
3. **Pseudostratified.** It contains columnar cells extending from the basement membrane to the surface of the epithelium (i.e. a single layer of tall cells) whereas the other cells fall short of the surface and are crowded among the bases of the columnar cells, forming two or more layers.
   a. **Columnar** (female urethra).
   b. **Ciliated.** The tall cells have motile cilia (respiratory passages).
   c. **Stereociliated.** The cilia are non-motile (epididymis).

C. Transitional epithelium. The number of cell layers varies according to the degree of contraction of the organs in which it occurs (ureter, bladder).

1. When contracted it consists of several layers and resembles closely the stratified epithelium, but the superficial cells are larger and have a convex free surface.
2. If stretched there are usually two layers: a deep layer of more or less cuboidal cells, and a superficial layer of large flattened cells.

II. Glandular Epithelium

Composed of secretory cells which show a definite polarity: the lower (basal) half contains the nucleus, the upper (apical) half is filled with granules or droplets of secretion.

The secretion may leave the cell as a fluid which crosses the permeable cell membrane: merocrine type (the most widespread); or in leaving it may destroy the membrane and surface protoplasm: apocrine type (mammary gland and armpit glands); or lastly, the secretion is not released until the cell dies and disintegrates: holocrine type (sebaceous glands). In the latter type there is constant replacement of the dead cells by new ones.

A. Exocrine (external secreting) glands. The secretion flows out through a duct which may open on the body surface (glands of the skin, mammary gland) or in cavities which communicate with the outside (glands of the alimentary canal, kidney, etc.).

1. Unicellular glands. Cells scattered among the elements of an epithelium; they usually secrete mucus.

a. Typical is the goblet cell of the intestine, respiratory mucosa, etc.

2. Multicellular glands. The epithelial secretory cells are arranged in various ways, as for instance, straight or coiled tubules, branched tubules, or in small vesicles (acini or alveoli).

a. Simple. The secretory units open directly on the surface of an epithelium (intestinal and sweat glands) or they open into a single simple duct (glands of the stomach, uterus, etc.).

b. Compound. The secretory units are much more numerous and are grouped into lobules more or less completely separated by connective tissue septa. The ducts of each lobule converge into larger ducts and the latter finally open into a main duct (salivary glands, lacrimal gland, etc.).

B. Endocrine (internal secreting) glands. These lack ducts; their secretions (called hormones) enter the blood stream after crossing the walls of the capillaries of the gland.

1. The glandular epithelium is arranged into vesicles (thyroid) or it forms irregular anastomosing strands (parathyroids, anterior pituitary, suprarenals).

C. Exo-endocrine glands. Compound glands with external and internal secretions. The endocrine portion may be represented by cell groups (islands of Langerhans of pancreas); or the gland cells may produce an external secretion conveyed by ducts and an internal passing directly into the blood (liver).

III. Neuroepithelium

Formed by cells adapted to receive stimuli which they transmit to sensory nerve endings. The free surface of the cells may have stiff cilia (cells of organ of Corti, maculae and cristae of the inner ear; gustatory cells). The epithelioid cells of certain chemoreceptors (carotid glomus, aortic bodies, p. 29) are probably neuroepithelium. (The cones and rods of the retina and the olfactory cells are modified nerve cells.)

BLOOD AND LYMPH

I. Blood

A tissue with fluid intercellular substance (blood plasma); the cell elements are: erythrocytes (red blood corpuscles) and leucocytes (white blood corpuscles). There are also non-nucleated corpuscles, the platelets.

A. Erythrocytes. In mammals they are biconcave discs measuring from 7.5 to 7.7μ. The central, thin area was formerly occupied by the nucleus. Remnants of the latter are occasionally seen (Howell-Jolly bodies). Contain hemoglobin. There are normally 4½ to 5 millions per cubic millimeter.

B. Leucocytes. Nucleated cells, much less numerous (5000 to 9000 per c. mm. in the human adult). Some lack granules in their cytoplasm (agranulocytes), while others have abundant granulations (granular leucocytes or granulocytes).

1. Agranulocytes.

a. Lymphocytes. Their size varies between 6μ (small) and 8-9μ (large lymphocytes). Nucleus round or slightly irregular, with heavy chromatin blocks. Basophilic cytoplasm. Ameboid but non-phagocytic. 20-25% of total leucocyte count.

b. Monocytes (large mononuclears). Larger than the preceding (9 to 12μ). Nucleus often kidney-shaped. Abundant, slightly basophilic cytoplasm with occasional granules. Non-phagocytic while in the blood stream. 3-8% of leucocyte count.

2. Granulocytes.

a. Neutrophils (also called polymorphonuclears or simply 'polys'). Ameboid cells (10-12μ) with very irregular, deeply staining nucleus and cytoplasm containing pale violet or lilac

granules. Most abundant of the leucocytes (65 to 75%); they ingest small foreign particles and bacteria.

b. Acidophils or eosinophils. Rarer than the preceding (2 to 5%). Nucleus not so irregular, often bilobed. Cytoplasm filled with granules stained with acid dyes.

c. Basophils. Rarest of all (0.5%). Granules are irregular, strongly basophilic. Nucleus irregular, lightly stained. Regarded by some as degenerative forms.

C. Platelets. Small (about 3μ), flattened non-nucleated bodies with a central granular area (endoplasm) and a rim without granules (ectoplasm). They appear as clusters in smears and are supposed to play a part in blood clotting.

D. Formation of the blood (hemopoiesis). In the embryo blood arises first in the wall of the yolk sac, then in the liver and spleen and, finally, in the bone marrow. Most blood cells in the yolk sac and liver are erythrocytes. Blood is formed in the adult in the bone marrow but most lymphocytes arise elsewhere (see lymph).

1. Erythropoiesis: formation of erythrocytes. The chief stages are:

a. Basophilic erythroblasts. They are the source of the erythrocytes in the adult. Cells with basophilic cytoplasm and heavy chromatin blocks in the nucleus (checker-board appearance). Divide.

b. Normoblasts. Smaller than the preceding and slightly larger than the erythrocytes. Small, deeply stained nucleus. Hemoglobin present in the cytoplasm. The younger normoblasts are still capable of division.

c. Erythrocytes arise through loss of the nuclei of the normoblasts. The dense, pyknotic nucleus may be extruded or it breaks up into particles which gradually disappear.

2. Leucopoiesis: production of leucocytes. The granulocytes pass through the following stages:

a. Myeloblasts. Basophilic cells with large nucleus containing a chromatin network and one or more large, compound nucleoli. Abound in fetal and young marrow; rarer in the adult. Divide by mitosis.

b. Myelocytes. Cells with roundish nucleus and a larger amount of cytoplasm containing granules which may be eosinophilic, basophilic or neutrophilic. Divide by mitosis; present in large numbers in adult marrow.

c. Metamyelocytes. Immature granulocytes with horseshoe-shaped nucleus, occasionally seen in the blood, especially in infections. They change into granulocytes.

3. **Formation of the monocytes.** This is a much debated question.

a. Some authors suppose that they are derived from specific cells (monoblasts) in the bone marrow.

b. Others see their origin in endothelium or in mesenchyme.

c. A third view is that they arise from lymphocytes in venous sinuses in the spleen, bone marrow, liver, etc.

4. **Formation of the platelets.** These arise through fragmentation of giant cells called megakaryocytes (see bone marrow; p. 18).

II. Lymph

A. Composition. A colorless fluid collected from all over the body and normally containing variable numbers of small lymphocytes. A few granulocytes (mostly eosinophils) may occur. The lymph from the small intestine contains much fat and has a milky appearance during digestion; it is then known as chyle.

B. Formation of the lymphocytes (lymphopoiesis). Lymphocytes arise in large numbers in the lymph nodes, spleen, thymus, and in patches of lymphoid elements in diverse organs. The following stages are recognizable:

1. **Medium-sized lymphocytes.** Cells with relatively large nucleus, containing one or more nucleoli. Basophilic cytoplasm. Divide by mitosis giving rise to small lymphocytes.
2. **Large lymphocytes (lymphoblasts).** Regarded generally as hypertrophied small lymphocytes; produce lymphocytes of smaller sizes through mitotic division. They may be scattered or grouped into 'germinal centers' (p. 41).

THE SUPPORTING TISSUES

They constitute the framework of the body. They are: connective tissue, reticulo-endothelium, cartilage and bone. They are all of mesodermic origin.

I. Connective Tissue

Present in all organs. Its characteristic cells are fibroblasts (or fibrocytes) separated by variable amounts of intercellular substance

containing fibers. The latter may be moderately abundant, loose connective tissue; or they may predominate, fibrous connective tissue.

A. **Loose connective tissue.** Fibroblasts and other cell types present.

1. **Fibroblasts.** Rather fixed, flattened, irregularly branched cells with large nucleus. Non-phagocytic.

2. **Fibers.** Produced through activity of the fibroblasts.

a. **Collagenous.** Bundles of fine fibrils held together by a cementing substance. They vary in size and anastomose freely. They yield gelatin when boiled with water.

b. **Argyrophil.** An extension of the preceding in areas in which cells are closely placed. They are impregnated with silver, hence their name. May change into collagenous fibers.

c. **Elastic.** Homogeneous, branched fibers anastomosed into loose networks. They are highly refractive and thinner than the collagenous.

3. **Ground substance.** Believed to be a system of thin membranes delimiting irregular spaces filled with fluid which increases in edema.

4. **Other cell types.**

a. **Leucocytes** migrated from the blood.

b. **Resting and wandering histiocytes.** When resting they have ragged outlines; nucleus smaller than in the fibroblast. Become ameboid and phagocytic in inflammation and engulf foreign matter (macrophages).

c. **Mast cells.** Irregular elements with small nucleus and cytoplasm loaded with strong basophilic granules. Normally rare.

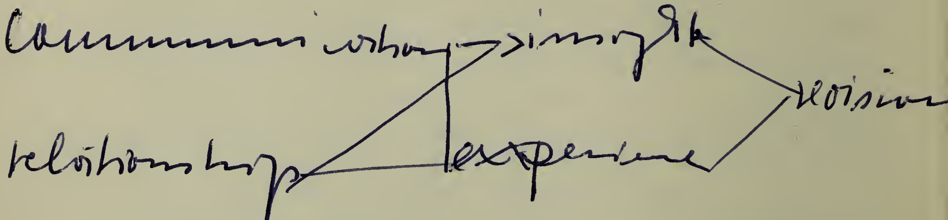
d. **Plasma cells (plasmocytes).** Also rare except in certain locations and in chronic inflammations. One or two nuclei closely resembling the nucleus of the lymphocyte, from which they may arise. Basophilic cytoplasm. Non-phagocytic.

e. **Fat cells.** Fat may appear as independent droplets or the latter merge into a single large drop which fills the cell. When very abundant they form adipose tissue.

B. **Fibrous connective tissue.** The cells present are mostly fibroblasts. The fibers are very abundant, the intercellular spaces very much reduced. The collagen or the elastic fibers may predominate.

1. **Mostly collagenous.** The bundles may be arranged regularly (tendons, ligaments, aponeuroses and fasciae) or irregularly

therapeutic process based on the communications in a special relationship.



(dense connective tissue). Whitish aspect due to abundance of collagen.

a. Tendons and ligaments. Thick, closely placed and parallel collagenous bundles. The fibroblasts appear as rows between the bundles and are very much compressed. The arrangement of the bundles is less regular in the ligaments.

b. Aponeuroses and fasciae. Bundles woven into a very compact meshwork containing also elastic fibers. Fibroblasts and other connective tissue cells present (derma of skin, sclera of the eye, periosteum, submucosa of alimentary canal, etc.).

2. Mostly elastic. Less frequent than preceding. Has yellowish color. The fibers form parallel strands with frequent anastomoses (ligamenta flava of the vertebrae, stylohyoid ligament, ligamentum nuchae, etc.).

II. Reticulo-endothelium

It consists of two closely associated parts: a meshwork of argyrophil fibers (reticulum) and fixed and wandering histiocytes. The latter are often flattened and contribute to the lining of the lymph and blood channels, thus resembling endothelial cells. Since endothelium is not phagocytic the term given to this close association of elements is a misnomer. Reticulo-endothelium forms the framework of the lymph nodes, spleen, bone marrow and liver; it also occurs in some endocrines (pituitary, adrenal), the uterine mucosa, skin, etc.

A. Reticulum. The argyrophil fibers vary in diameter and are repeatedly anastomosed. They are continuous with the collagen fibers.

B. Histiocytes (clasmatocytes, macrophages). They are identical with the resting and wandering histiocytes of loose connective tissue. The resting cells may become ameboid and ingest bacteria, foreign particles and degenerated cells.

1. Resting histiocytes. They are either anchored to the reticulum (which they may partly envelop with their prolongations), or they lie among the argyrophil fibers. According to their location they have received special names:

a. Reticular cells. Occur in the lymph nodes.

b. Splenocytes. Present in large numbers in the red pulp of the spleen.

c. Kupffer cells. Scattered among the endothelial cells lining the liver sinusoids.

d. Adventitial cells. In the externa (or adventitia) of the smaller vessels of the body.

2. **Wandering histiocytes.** Ameboid cells resembling the blood monocytes; their nuclei are often kidney-shaped. They may phagocytose whole cells (erythrocytes, lymphocytes, etc.).

C. Other cell types. Undifferentiated (mesenchyme) cells and fibroblasts also occur associated with the reticulum.

D. Functions. Reticulo-endothelium is an important part of the defenses of the body. Besides being phagocytic its cells are supposed to produce antibodies. The latter activity is said to be diminished when the cells are loaded with ingested particles (India ink, lithium carmine, etc.). This is called 'blockage' of the reticulo-endothelial system.

III. Cartilage

Consists of roundish cells (chondrocytes) separated by a solid intercellular substance which may become calcified in the adult. Cartilage is surrounded by a layer of dense connective tissue (perichondrium) and transitions between its fibroblasts and the superficial chondrocytes are found. It lacks vessels of its own, as well as nerves.

The ground substance has a homogeneous, glassy aspect (hyaline cartilage) or is occupied by elastic networks (elastic cartilage). In a third variety the cells occur as elongated groups separated by collagenous bundles (fibrocartilage).

A. Hyaline cartilage. It has a distinct whitish color when fresh. When boiled with water yields gelatin.

1. **Cells.** Although usually spherical they may be flattened through mutual pressure. The cells in the surface are also flattened. The nucleus is rather large and the cytoplasm contains glycogen, fat droplets and vacuoles.

2. **Ground substance.** It has cavities or lacunae occupied by the chondrocytes, and numerous fibrils.

a. Lacunae. Each lacuna is normally occupied by a single chondrocyte. In the adult the lacunae usually occur in groups corresponding to cells derived by division of a single chondrocyte (isogenic groups).

b. Capsule. This is distinct layer around each lacuna; it differs

from the rest of the ground substance in that it is more refractile and stains more deeply.

c. Fibrils. Although the ground substance is apparently homogeneous it contains a close meshwork of fine collagenous fibrils visible only after digestion with trypsin or impregnation with certain silver techniques.

3. Distribution. Hyaline cartilage is the most typical and widespread. It forms most of the embryonic skeleton and is later replaced by bone except in certain places (ventral end of the ribs, articular surfaces of all bones). It also occurs in the nose, larynx, trachea and bronchial tree.

B. Elastic cartilage.

1. Cells. They do not differ from those in the preceding variety.

2. Ground substance. It also has lacunae bounded by capsules. It contains elastic networks which may be very dense and are continuous with the elastic fibers of the perichondrium.

a. The abundance of elastic fibers imparts a yellowish color to this variety of cartilage.

3. Distribution. Elastic cartilage is not so common as the hyaline variety. It is found in the pinna of the ear, external auditory meatus and eustachian tubes, epiglottis, certain cartilages of the larynx, etc.

C. Fibrocartilage. It is a transition between the dense connective tissue of tendons and ligaments and the hyaline cartilage. Accordingly its cells tend to form rows. It lacks a true perichondrium.

1. Cells. They are spherical or slightly elongated.

2. Ground substance. The poorly developed, hyaline ground substance may be condensed as a capsule around each cell. The cell groups are separated from each other by collagenous bundles continuous with those of the tendon or ligament.

3. Distribution. It is found in the interarticular cartilages (lower jaw, knee, clavicle), intervertebral disks, symphysis pubis and some other locations.

IV. Bone

Bone is a tissue consisting of branched cells (osteocytes) separated by a fibrillar intercellular substance hardened by calcium salts. It forms the greater part of the mammalian skeleton.

A. **Structure.**

1. **Osteocytes.** Cells with rather large, deeply stained nucleus and faintly basophilic cytoplasm continued into branched, freely anastomosing processes.
2. **Lacunae.** Each osteocyte is contained within a lacuna, which it fills completely. From the lacuna arise fine canals (bone canalicules) which contain the processes of the osteocyte. Around each lacuna there is a thin capsule.
3. **Interstitial substance.** Apparently homogeneous but actually formed by thin bundles of fibers (osteocollagenous fibers) which yield gelatin when boiled with water. They can be demonstrated by silver impregnation.
   a. The osteocollagenous fibers are cemented together by an amorphous substance.
   b. Removal of the calcium salts by weak acid solutions (decalcification) leaves the organic portion intact.
4. **Mineral substance.** According to most authors the calcium deposits occur only in the amorphous substance binding the osteocollagenous fibers. The calcium is present mostly as dahllite ($Ca\ Co_3.2Ca_3(PO_4)_2$). The abundance of calcium salts causes the bone to retain its shape and structure after maceration. In thin plates of dry bone the empty lacunae and the canalicules can be readily recognized.

B. **Types of bone.** Bone may have a spongy or a compact appearance. In long bones the shaft or diaphysis consists chiefly of compact bone inclosing a large marrow cavity, while the epiphyses are made of spongy bone with a thin, peripheral layer of compact bone. Short bones closely resemble the epiphyses.

1. **Spongy (cancellous) bone.** Bone is first laid down as a framework of anastomosing trabeculae. The intertrabecular spaces are occupied by marrow. Bone-forming cells (osteoblasts) and bone-destroying elements (osteoclasts) are often seen on the surface of the trabeculae.
2. **Compact bone.** The interstitial substance is divided into regularly arranged, thin bony plates or lamellae; this arrangement is closely connected with the distribution of the blood vessels which supply the bone.
   a. **Haversian systems.** An Haversian system contains a small central canal occupied by small blood vessels and lymphatics.

(1) The canal is surrounded by a number of concentrically arranged, thin lamellae (4 to 20 or more) appearing as rings in cross section.

(2) The direction of the osteocollagenous fibrils is different in each lamella since they run spirally to the axis of the Haversian canal, each spiral being independent from those in adjacent lamellae.

(3) In and between the lamellae there are osteocytes, and their anastomosing canalicules open into the canal. The canals branch and anastomose with each other.

b. Interstitial lamellae. They fill the spaces between the Haversian systems. Most of them are the remnants of these systems after partial destruction during bone formation.

c. Circumferential lamellae. They occur on the external surface of compact bone and on the wall of the marrow cavity of long bones. They also contain osteocytes enclosed within lacunae.

d. Sharpey's (perforating) fibers. These are collagenous bundles of varying thickness which enter the compact bone from the periosteum.

e. Volkmann's canals. Vascular branches from the periosteum enter through these thin tunnels, which are not surrounded by concentric lamellae. They connect with the Haversian canals.

C. The bones as organs. Closely associated with the bone tissue proper are:

1. Periosteum. A dense connective tissue envelope firmly attached to the surface of the bone. It is absent in the articular surfaces and the inner surface of the cranial bones. It consists of two layers:

a. An outer (vascular) layer of dense connective tissue rich in blood vessels and containing also lymphatics and nerves. Branches of these vessels enter the bone through Volkmann's canals.

b. An inner (fibrous) layer of collagenous and elastic fibers. The cells in this layer are flattened and under certain conditions (i.e. after fractures) they give rise to osteoblasts and osteoclasts. The former abound in the embryo and young in which they may form a third (osteoblastic) layer.

2. Endosteum. A thin connective tissue layer lining the larger bone cavities, especially the central (marrow) cavity in long bones.

3. Bone marrow. Fills the cavities of the bones. It consists of a

reticulo-endothelial framework continuous with the endosteum. The meshes of the framework contain:

a. Numerous thin-walled vessels.

b. Megakaryocytes. Giant cells with very irregular, often ring-shaped, large nucleus which stains deeply. Cytoplasm with a central granular portion (endoplasm) and a non-granular superficial layer (ectoplasm). Megakaryocytes are the source of the blood platelets (p. 10).

c. Intermediate stages in the formation of the blood cells (p. 10).

d. Fat cells. Abound in the adult, especially in the shaft of the long bones where the marrow is really adipose tissue (yellow marrow). The blood-producing (red) marrow remains throughout life in the epiphyses of the long bones and in the vertebrae, ribs, sternum and base of the skull.

D. Formation of bone (osteogenesis). Bone tissue is laid down relatively late in fetal life. Previous to this the skeleton consists of hyaline cartilage. The latter is then replaced by bone (endochondral ossification) but certain bones may arise directly from mesenchymal tissue (intramembranous ossification).

1. Intramembranous ossification. The bones of the vault of the cranium, the flat bones of the face, and the jaw (membrane bones) arise by this method.

a. Formation of the osteoblasts. Mesenchymal cells are changed into these without losing their processes, but their cytoplasm becomes decidedly basophilic and the nucleus excentric. Between the modified mesenchyme cells there are delicate bundles of collagenous fibrils.

b. Deposition of intercellular substance. The osteoblasts deposit fibrillar bone in the form of anastomosing trabeculae, which increase in size through the activity of newly formed osteoblasts and division of preexisting ones.

c. Formation of the osteocytes. Numbers of osteoblasts become imprisoned within the trabeculae to form the osteocytes of mature bone.

d. Calcification. The newly formed trabeculae soon become calcified.

2. Endochondral (intracartilaginous) ossification. This implies the removal of the preexisting cartilage and its replacement by

bone. Accordingly, the first stages (a-d) are those of degeneration of the cartilage.

a. **Hypertrophy of the chondrocytes.** The cartilage cells (chondrocytes) and the lacunae become much larger, with a corresponding decrease in the amount of intercellular substance. Many of the enlarged lacunae become confluent.

b. **Degeneration of the chondrocytes.** After their initial hypertrophy the chondrocytes shrink and finally disappear.

c. **Calcification of the remaining ground substance.** The strips of ground substance between the groups of confluent lacunae—which form parallel rows in the diaphyses of the long bones—become calcified.

d. **Formation of the primordial marrow cavities.** They arise through further merging of the enlarged lacunae and will be occupied by the marrow and numerous blood vessels.

e. **Penetration of the osteomyelogenic mesenchyme.** During the preceding stage the innermost of the layers of the fetal periosteum forms buds which corrode the peripheral portion of the cartilage, bringing into the primordial marrow cavities mesenchymal elements which will give rise to osteoblasts and cells of the primitive bone marrow, respectively.

f. **Penetration of the blood vessels.** Vascular loops and buds from the periosteal vessels also grow rapidly within the primordial marrow cavities. In long bones they advance toward the ephiphyses which are ossified independently from the diaphysis.

g. **Formation of the osteoblasts.** The mesenchyme cells near the surface of the bars of calcified cartilage become osteoblasts, which are cells of various shapes with basophilic cytoplasm and excentric nucleus. Slender prolongations may arise from their cytoplasm.

h. **Deposition of osteoid.** The osteoblasts arrange themselves into an irregular layer on the surface of the strips of calcified cartilage and deposit soft bone. Those which remain imprisoned within the latter become osteocytes. The osteoid or pre-osteal substance soon becomes calcified.

i. **Absorption of the newly-formed bone.** During fetal life and also in early post-natal life growth of the bones is continuous. To avoid massiveness and permit enlargement of the primordial marrow cavities there is a process of destruction and recon-

struction of the bone. Destruction is effected by the osteoclasts which are cells with acidophilic cytoplasm containing several nuclei (up to 20 or more). They are seen in contact with the surface of the bony trabeculae.

j. Periosteal ossification. Osteoid is laid down in the periphery by the osteoblasts of the inner layer of the periosteum. In long bones a collar or cylinder of osteoid is formed around the diaphysis even before the buds of osteomyelogenic mesenchyme have penetrated the degenerated cartilage. Most of the compact bone is formed this way.

k. Epiphyseal ossification. The epiphyseal ossification does not begin until about the time of birth. The osteomyelogenic mesenchyme reaches the center of the epiphyseal cartilage from the diaphysis. Spongy bone is formed by the osteoblasts. Between the epiphysis and the diaphysis there is a line of actively growing cartilage (epiphyseal line or synchondrosis) which maintains the growth of the bone in length until it is terminated in adult life.

MUSCULAR TISSUE

Muscular tissue consists of much elongated cells (muscle fibers) differentiated for contractility. The latter is practically limited to one direction, the long axis of the cell. The contractile elements are special fibrils (myofibrils) which develop within the embryonic muscle cells or myoblasts.

Three varieties occur in the adult: Smooth, striated (skeletal) and cardiac muscle, respectively. With few exceptions (iris of the eye, sweat glands) muscular tissue arises from mesoderm.

I. Smooth Muscle

Smooth muscle fibers are long spindles (20 to 500μ) with centrally placed nuclei. They abound in the arteries, alimentary canal, bladder, uterus, etc.

A. Structure.

1. Cell membrane. It is indistinct. Intercellular bridges connecting the cells are known to occur.

2. Sarcoplasm. The cytoplasm or sarcoplasm is occupied by numerous myofibrils. The latter are long, slender filaments of a

homogeneous substance; those in the periphery are coarser (border or external fibrils). The myofibrils are barely visible in routine preparations.

3. **Nucleus.** Its shape varies according to the degree of contraction of the fiber. If the latter is relaxed the nucleus is almost cylindrical. In much contracted fibers it appears lobulated or even twisted. It has a pale chromatin network and one or more nucleoli.

B. Appearance in sections. Smooth muscle fibers are either scattered or they form definite bundles and layers. The direction of the fibers is the same in each bundle or layer. Since the thick middle portions of the fibers (containing the nucleus) do not lie at the same level, a cross section of a bundle will show only a few nuclei and many non-nucleated portions, i.e. sections of the tapering portions of adjacent fibers.

C. Development. Smooth muscle arises from myoblasts in the visceral or splanchnic layer of the mesoderm (p. 109). The early myoblast is a short spindle-shaped cell containing cytoplasmic granules which gradually merge to form the myofibrils.

II. Striated (Skeletal) Muscle

The fibers are long (1 to 40 mm.), contain many peripherally placed nuclei and numerous myofibrils composed of alternating light and dark disks; the latter cause the cross-striated appearance.

A. Structure.

1. **Cell membrane (sarcolemma).** A very thin, structureless membrane which envelops the fiber.

2. **Sarcoplasm.** It fills the spaces between the numerous myofibrils. It is best seen around the nuclei. According to the amount of sarcoplasm two varieties of fibers (mixed in the human muscles) can be differentiated:

   a. **Red fibers.** These are rich in sarcoplasm and relatively poor in myofibrils. Their color is due to the presence of a diffuse, red pigment. They are less easily fatigued than the following.

   b. **White fibers.** They contain less sarcoplasm; the myofibrils are more numerous and thinner. They predominate in the least active muscles.

3. **Myofibrils.** They are clearly visible, especially in cross sections of the fibers in which they appear as dots, evenly distributed or grouped into polygonal areas (fields of Conheim) separated from

each other by tracts of sarcoplasm. They consist of alternating dark and light disks.

a. **Dark or anisotropic disk.** Made of double-refractive substance which is bisected by a narrow light disk (disk of Hensen).

b. **Light, single-refractive (isotropic) disk.** It is likewise bisected by a thin, dark band: the membrane of Krause or telophragm. Krause's membrane, however, forms a transverse partition across the whole fiber and is united with the sarcolemma peripherally.

c. **Sarcomeres.** These are the portions of the myofibrils between two membranes of Krause.

4. **Nuclei.** Their number depends roughly on the length of the fiber and may reach several hundred. In fully developed fibers they are always found in the periphery, under the sarcolemma; in the muscle fibers of infants and in some red fibers a few centrally placed nuclei may be seen. The nuclei are oval or elliptical and have one or more nucleoli.

5. **Motor plates.** These correspond to the areas of termination of motor nerve fibers on the muscle. Normally there is one plate for each fiber, placed midway between the ends or closer to one end (tongue). The motor plate causes a swelling on the surface of the fiber and is partially surrounded by nuclei (p. 28).

B. Development. Striated muscles arise from the embryonic myotomes (see p. 109). The latter consist of spindle-shaped myoblasts, each of which has at first a single nucleus.

1. **Formation of the myofibrils.** They appear first as homogeneous threads, but they soon show thickenings, the forerunners of the anisotropic disks. They increase in numbers through splitting.

2. **Nuclear multiplication.** Through repeated divisions numerous nuclei are formed. They appear as a row in the center of the fiber, while the periphery is occupied by the myofibrils. In the meantime the fiber becomes elongated.

3. **Migration of the nuclei.** The nuclei finally migrate toward the periphery while the myofibrils move toward the center of the fiber.

4. **Fusion of fibers.** According to some authors a striated muscle fiber is not a single, elongated cell but a syncytium arising through fusion of several myoblasts. In this way greater length is attained.

C. The skeletal muscles as organs. Muscles are formed of large numbers of parallel muscle fibers bound together by connective tissue. The fibers are grouped into primary bundles, several of which form secondary bundles, etc.

1. **Epimysium.** This is a sheath of connective tissue (also known as the external perimysium) enveloping the muscle.
2. **Perimysium.** Partitions arising from the epimysium enter the body of the muscle.
3. **Endomysium.** Represented by the connective tissue which separates the muscle fibers within the primary bundles.
4. **Muscle-spindles.** These are groups of poorly differentiated muscle fibers enclosed within a connective tissue sheath. The latter is perforated by one or more sensory nerve fibers which end around the muscle fibers (p. 29).
5. **Muscle-tendon junction.** Many histologists believe that there is no transition between the muscle fibers and the collagenous bundles of the tendon; the former end abruptly, their rounded ends being covered by the sarcolemma to which are attached the collagenous fibers. This view is not held by others.

III. Cardiac Muscle

The characteristic muscle of the heart is striated but it differs from skeletal muscle in that it is formed by repeatedly anastomosed fibers (really a syncytium). The nuclei are centrally placed in the syncytial strands.

A. Structure.

1. **Sarcolemma.** It is a delicate membrane best seen in longitudinal sections of contracted fibers.
2. **Sarcoplasm.** It fills the spaces between the myofibrils; it is more abundant near the poles of the nucleus where it usually has granules of pale yellow pigment increasing with age.
3. **Myofibrils.** They are coarser than in skeletal muscle and have the same structure. Krause's membrane is also present.
4. **Nuclei.** The nuclei are oval, but may appear irregular in cases of extreme contraction.
5. **Intercalated disks.** Either straight bands, or V-shaped stripes or a group of disks arranged like steps, highly characteristic of cardiac muscle. They are usually indistinct in routine slides, but can be brought out with certain dyes.

a. They were formerly regarded as the thickened membranes at the end of the fibers; however several intercalated disks may occur in close proximity, without nuclei in between.

b. Their function is unknown.

B. Development. Cardiac muscle tissue is derived from the splanchnic mesoderm in contact with the cardiac tubes (p. 133). The myoblasts are at first independent but they soon merge into a syncytium; the nuclei multiply and the myofibrils arise as in skeletal muscle. A lesser degree of differentiation is characteristic of the muscular portions which become the conductive system of the heart (p. 39).

NERVOUS TISSUE

Nerve cells are built for the reception of stimuli and their transmission to other nerve cells or to diverse structures (musculature, glands, etc.). They are the most highly specialized cells of the body. Nervous tissue consists of two different elements: the nerve cells or neurones, and the supporting tissue or neuroglia, respectively.

I. Nerve Cells (Neurones)

A typical nerve cell has branched processes arising from the cell body or perikaryon. One of these, called the axon, carries impulses away from the cell body (i.e. centrifugally) while the others, known as dendrites, generally receive impulses which they transmit in the opposite direction (i.e. centripetally).

A. Shape. The shape of the nerve cell is highly variable, as well as its size. According to the number and position of the processes three main types are recognized:

1. Multipolar. Has one axon and several dendrites.

2. Bipolar. Only two processes, one of which is a dendrite, the other the axon (retina; ganglia of the inner ear).

3. Monopolar. The single process soon bifurcates: one branch corresponds to the dendrite (i.e. it transmits centripetally), the other is the axon (most cells of the cerebrospinal ganglia except those noted above).

4. Transitions between 2 and 3 are of common occurrence in the cerebrospinal ganglia.

5. Dendrites. They may be poorly or profusely branched. In many

cells they are beset with very small spiny-like processes (gemmules).

6. **Axon.** The axon or axis-cylinder is a thin, smooth process of variable length. It gives off branches roughly at right angles to its axis (collaterals) and ends in a tuft of branches (terminal arborization).

   a. **Short axon type.** The axon breaks up into numerous branches near its emergence from the cell body.

   b. **Long axon type.** The terminal arborization occurs at a variable distance from the cell body (a few millimeters to many inches).

7. **Neurone theory.** A nerve cell, including its dendrites and axon, is regarded by most histologists as a unit or entity, termed neurone.

   a. The neurone theory claims a lack of continuity between the processes of one neurone and those of another.

   b. According to this view the nervous system consists of chains of independent neurones associated with each other in various ways.

B. Structure.

1. **Cytoplasm (neuroplasm).** A homogeneous, semiliquid and highly viscid substance which occupies the entire neurone. In the axon it is called axoplasm. A cell membrane is absent.

2. **Neurofibrils.** Threads of variable thickness (seen in the living) which run in every direction and extend into the dendrites and axon to the finest terminal twigs. They anastomose frequently to form an elaborate meshwork within the cell.

   a. Neurofibrils are impregnated with silver techniques (neurofibrillar methods).

   b. They have been regarded by some as the substratum for transmission of nervous impulses, while others consider them as a supporting framework of the neurone.

3. **Chromophilic (tigroid) substance.** Occurs in large and medium-sized (chromophilic) neurones.

   a. **Structure.** It consists of granules clumped together into masses of various sizes (Nissl bodies). The granules stain deeply with basic aniline dyes. They are, most probably, preexisting structures, not artifacts, which occupy the meshes of the neurofibrillar framework.

b. Distribution. When present, the Nissl bodies occur not only in the cell body but also in the dendrites; they are absent in the axon and the point of its implantation on the cell body (axon hillock).

(1) The form, size and distribution of the Nissl bodies is extremely variable in different cells and may be related to variations in the density of the neurofibrillar meshwork.

c. Changes. Nissl bodies decrease in numbers and even disappear in fatigued nerve cells and in certain pathological processes (chromatolysis). They are similarly affected after injury to the axon.

4. Nucleus. The nucleus is roughly spherical and relatively large, specially in the motor neurones of the spinal cord. Its structure varies according to whether the neurone is chromophilic or chromophobic (i.e. lacks Nissl bodies).

a. Chromophilic neurones. The large nucleus contains a linin meshwork (p. 2), abundant nuclear sap and a large nucleolus (rarely two or more). The chromatin is scanty, being represented by one or two dense, small masses near the nucleolus.

b. Chromophobic neurones. In small and many medium-sized neurones the chromatin is scattered over the linin meshwork or forms large knots.

5. Organoids and inclusions. Nerve cells possess a well-developed Golgi apparatus and mitochondria. Inclusions are represented chiefly by a yellowish pigment (lipochrome), to which the color of the gray matter is due. This type of pigment increases with age. Melanin occurs only in certain areas of the central nervous system and in the neurones of the cerebrospinal and sympathetic ganglia.

6. Cytocentrum. Although adult nerve cells do not divide a cytocentrum containing two centrioles of unequal size and shape has been described.

C. Nerve fibers. Since axons are the chief constituents of the peripheral nerves they are called nerve fibers, a term also used for the long axons within the central nervous system. In the peripheral nerves axons are always enclosed within sheaths; in the central nervous system there are both sheathed and naked axons.

1. Structure of the axon. It contains numerous neurofibrils placed so closely that they cannot be identified as such except in thick

axons. Thin axons always show a compact structure. The neurofibrils in either case may be seen in the branches of termination.

2. Sheath of Schwann or neurilemma. Present in the peripheral nerves. It is a delicate membrane consisting of a single layer of flattened, branched cells (cells of Schwann); the branches wrap themselves around the axon.

a. They are not of connective tissue nature but probably belong to neuroglia (see p. 33).

b. They are important as nutritive elements for the axon and also play an active part during nerve regeneration.

3. Myelin sheath. Occurs in the peripheral nerves and also in the central nervous system. It is an homogeneous envelope made up of a mixture of various lipoids (of which cholesterol is the most important), certain cerebrosides, phospholipins and fatty acids.

a. Nodes of Ranvier. In the central nervous system the myelin sheath is practically continuous. In peripheral nerves it is divided into segments by constrictions, called nodes of Ranvier. The thicker the axon the longer the segments.

b. Clefts of Schmidt-Lantermann. The myelin of each segment is practically interrupted by oblique clefts; the segment is thus divided into funnel-shaped sections.

c. Relation of the Schwann cells to the myelin segments. Each myelin segment is surrounded by a single cell of Schwann. In thick fibers the nucleus of the Schwann cell usually appears within a shallow depression of the myelin segment.

4. Myelinated and unmyelinated fibers. The thickness of the myelin sheath is in direct ratio to the diameter of the axon. In very thin myelinated fibers the sheath is not visible unless it is stained. Unmyelinated fibers are grouped into small bundles enclosed within a syncytium of Schwann cells.

5. The nerves as organs. One or more bundles of nerve fibers enclosed within a connective tissue sheath is called a nerve. The bundles and the nerve fibers within them are bound together by connective tissue which carries the vessels for the nerve.

a. Epineurium. This is the outermost connective tissue sheath.

b. Perineurium. The sheath around each individual fascicle. When several fascicles occur (i.e. in the sciatic nerve) the space between the perineurium and the epineurium contains connective tissue and fat cells.

c. Endoneurium. Septa from the preceding, dividing the nerve fascicle into compartments, are known collectively as the endoneurium. The compartments are occupied by numerous nerve fibers.

d. Sheath of Key-Retzius. The nerve fibers are separated from each other by fine collagenous bundles which collectively form this sheath. A still finer sheath composed of delicate argyrophil fibers occurs in contact with the cells of Schwann.

D. Nerve endings. These are the terminations of the axons and their branches (collaterals). The endings may be located within the central nervous system and ganglia (see synapse) or in various tissues in diverse parts of the body. The latter will be considered here.

1. Efferent. They discharge nervous impulses on the muscle fibers, ganglia, and the cells of various glands.

a. Motor plates. Their position has already been indicated (p. 22). The nerve fiber ending within the plate loses its myelin before it crosses the sarcolemma. The (hypolemmal) ending has short, irregularly dilated branches; nuclei occur among them.

(1) The boundary between the plate and the sarcoplasm (the "sole") has nuclei belonging to the muscle fiber.

b. Diffuse motor endings. Found in the smooth musculature of various organs and in cardiac muscle. The terminal arborizations have long branches which touch the surface of the muscle fibers (epilemmal endings).

c. Secretory endings. Occur in contact with the secretory cells of certain glands (salivary and lacrimal gland, pancreas, etc.).

d. Preganglionic endings. Are located within the ganglia of the sympathetic and parasympathetic divisions of the autonomic system. They are the terminations of axons of neurones which reside in the spinal cord, medulla oblongata, and midbrain (p. 32).

2. Afferent. Afferent nerve endings receive impulses originating in various parts of the body, which they transmit to the central nervous system. They may be free (a-c) or encapsulated (d-h).

a. Intraepithelial endings. The terminal branches occur among the epithelial cells, usually in stratified (skin, sheath of hair follicle, cornea) and pseudostratified (respiratory) epithelia.

The terminal swellings may be very close to the epithelial surface.

b. Connective tissue endings. They occur mostly under epithelia (skin, cornea). They are usually diffuse.

c. Vascular endings. The best known are the pressoreceptors of the carotid sinus, arch of the aorta and base of the right subclavia; they are stimulated mechanically by changes in the blood pressure which stretch the vessel wall. Appear as elaborate arborizations with reticulated swellings in their branches. Also present in the large veins entering the heart.

d. End bulbs. Spherical or oval, with a thin connective tissue capsule which contains the twisted terminal arborizations of one or more sensory fibers. They occur in diverse areas of the body (conjunctiva of eye, lips and buccal mucosa, nasal cavities, external genitals, etc.).

e. Tactile corpuscles (of Meissner). More complex than the preceding. Oval bodies divided into compartments by horizontal septa attached to the capsule. The compartments contain the much twisted terminal branches of one or more sensory fibers.

(1) They occur in the skin, especially in the finger tips, palm of the hand, and sole of the foot.

f. Pacinian corpuscles. Usually large, laminated, elliptical structures. The capsule is formed by many concentrical lamellae of connective tissue nature. The axis is occupied by a cavity where a single nerve fiber ends without branching.

(1) Occur in the subcutaneous tissue in various parts of the body and in the mesenteries.

(2) They are stimulated by deep, or heavy, pressure.

g. Neuromuscular spindles. Already mentioned (p. 23). The sensory fibers branch profusely around the poorly differentiated muscle fibers, which they touch in many places.

(1) They are affected by stretching and also by extreme contraction of the muscle.

h. Muscle-tendon spindles. Occur at or near the junction of the muscle with the tendon. The spindle consists of several tendon bundles covered by a thin capsule. One or more sensory fibers enter the spindle, where they break into complicated arborizations. Function as the preceding.

i. Chemoreceptor endings. Occur in small organs formerly re-

garded as paraganglia (carotid and aortic glomus, supracardial paraganglia). The nerve terminals are in close contact with cells (probably neuroepithelial).

(1) They register changes in the oxygen content of the blood, which elicit respiratory reflexes.

E. Distribution of the neurones; their relations (synapse). Nerve cells are not scattered throughout the nervous system but occupy definite areas in the brain and spinal cord and outside these regions (i.e. in the ganglia).

1. Gray matter. Areas occupied by neurones are distinguished from other parts of the nervous system in that they have a distinct grayish color. This is due to the presence of pigment within the neurones (p. 26). The neurones may occur in groups or be arranged in layers. The gray matter contains not only the cell bodies but also the dendrites and a variable portion of the axons of the neurones.

a. Brain. In the cerebral hemispheres and the cerebellum the gray matter occurs in the periphery while the more central portions contain white matter with a number of gray masses or nuclei (basal nuclei of the brain; nuclei of cerebellum).

b. Spinal cord. The relations of the gray and white matter are reversed, i.e. the latter occurs in the periphery, the gray matter in the center. In cross section the gray matter roughly simulates an H.

2. White matter. It is formed by the axons of the neurones, which are myelinated, for the most part. Hence its color. The sheath of Schwann is absent but the axons are enveloped by the processes of the neuroglia cells, especially the oligodendroglia (p. 33).

3. Synapse. The neurones of the central nervous system are arranged in such a way that the termination of the axon of a neurone touches the cell body and dendrites of one or more neurones. This contact is called synapse. Synapses occur only in the gray matter.

a. Terminal buttons ('boutons terminaux'). They are thickenings of the finest axonic twigs in contact with the neurone.

b. Axosomatic synapses. The branches of the axon end in contact with the cell body of the neurone.

c. Axodendritic synapses. Contact is effected with the dendrites (climbing and mossy fibers of the cerebellum).

d. Mixed synapses. A neurone may receive impulses from several sources, some axons ending in contact with the cell body, others in contact with the dendrites (motor neurones of the spinal cord).

F. Structure of the ganglia. A ganglion is a collection of neurones in the path of a nerve. The neurones may receive impulses through a peripheral prolongation ending somewhere in the body (sensory or afferent neurones) or they may originate impulses which are projected on smooth and cardiac muscle, glands, etc. (autonomic neurones).

1. Cerebrospinal ganglia. The ganglia of some of the cranial nerves (trigeminus, facial, auditory, glossopharyngeus and vagus) and the spinal ganglia are sensory and have the same structure. They consist of monopolar neurones, except the cochlear and vestibular ganglia of the auditory nerve in which the neurones are bipolar. A few of the latter may occur in the other ganglia.

a. Distribution of the neurones. They form a continuous layer in the periphery of the ganglion; toward the center they are grouped into irregular strands separated by bundles of nerve fibers. The neurones vary considerably in size.

b. Structure. Sensory neurones have a neurofibrillar meshwork and Nissl bodies; the latter are well developed in the large neurones which have a vesicular nucleus, poor in chromatin (p. 26).

c. Processes.

(1) Bipolar cells. The peripheral process is usually thicker than the central process which enters the spinal cord. Both are myelinated, and in some cases the myelin sheath may also enclose the cell body.

(2) Monopolar cells. They have a single process which soon acquires a myelin sheath. It bifurcates into a peripheral branch and a thinner central branch entering the cord; both are myelinated in the larger cells.

d. Capsule. Each neurone is surrounded by a connective tissue capsule (continuous with the endoneurium) which is lined internally by flattened cells.

e. Satellite cells (amphicytes). These are branched elements residing within the capsule, in contact with the surface of the

neurone which they may corrode in old subjects. They are probably neuroglia cells.

f. Absence of synapses. Since sensory neurones do not receive impulses from other nerve cells there are no synapses in cerebrospinal ganglia.

2. Ganglia of the autonomic system. The sympathetic and parasympathetic ganglia have a similar structure. They consist of multipolar neurones of various sizes and shapes. The smallest of the parasympathetic ganglia may have only a few neurones.

a. Distribution of the neurones. Similar to that mentioned for the cerebrospinal ganglia.

b. Structure. Neurofibrillar meshwork and Nissl bodies are present. The latter are usually smaller and more diffuse than in the cerebrospinal ganglion cells. Binucleated neurones may occur.

c. Dendritic processes. The dendrites vary enormously in number, shape and length, as well as in the degrees of branching. In many ganglia the dendritic processes of several cells form bundles (protoplasmic tracts). Short (intracapsular) dendrites occur in the apes and in man.

d. Axon. Resembles closely a dendrite and does not give off collaterals. The thinner axons are unmyelinated (fibers of Remak). The myelin sheath around the thicker axons may be interrupted in stretches.

e. Capsule. Similar to the capsule of the cerebrospinal neurones but extending somewhat along the larger dendrites. In some small parasympathetic ganglia (plexuses of the intestine) the capsule is normally absent.

f. Satellite cells. Present in variable numbers.

g. Synapses. Since the autonomic ganglia receive impulses through preganglionic fibers they are the site of numerous synapses.

(1) The terminal twigs of the preganglionics end as buttons of variable size and, in many cases, as minute rings.

(2) Synaptic contact may take place with the dendrites or with the cell body; in the latter case the terminal branches, after crossing the capsule, wrap themselves around the cell (pericellular baskets).

II. Neuroglia

The supporting tissue of the central nervous system is known as neuroglia. It fills the spaces between the neurones and their dendrites, and also occurs between the axons; i.e. is present in the gray as well as in the white matter. Several varieties are recognized.

A. Ependyma. It has the appearance of a columnar epithelium. It lines the central canal of the spinal cord and the ventricles of the brain. The ependymal cells have basal processes which branch and penetrate more or less deeply in the surrounding (nervous) tissue. They contain specific (neuroglia) fibers, and are to be considered as neuroglia cells which have retained their embryonic shape and position (see p. 157).

B. Neuroglia proper. The cells are branched. Three varieties are recognized:

1. **Astroglia.** Made up of star-shaped cells (astrocytes) with numerous processes, some of which end on the walls of capillaries by means of conical or flattened swellings (vascular feet).
    a. **Protoplasmic astrocytes.** Their processes are relatively short and profusely divided. Ovoid nucleus with scant chromatin. The cell body and processes contain small, roundish granules called gliosomes.
        (1) Occur chiefly in the gray matter of the brain and cord.
    b. **Fibrous astrocytes.** The processes are much longer; they contain fibers ('glia' fibers) which extend into them for considerable distances. They also have gliosomes.
        (1) Found chiefly in the white matter.
2. **Oligodendroglia.** Smaller than the astrocytes, with relatively few processes which wrap themselves around the myelin sheaths of the axons. The nuclei are round and have small chromatin blocks. More abundant in the white than in the gray matter.
    a. The cells of the sheath of Schwann (p. 27) and the satellite cells of the ganglia are probably oligodendroglia.
3. **Microglia.** The smallest of the neuroglia. Their function is similar to that of the histiocytes of connective tissue. Evenly scattered in the white and gray matter, but they predominate in the latter.
    a. **Resting stage.** The nucleus is small, often irregular and

deeply stained. The cell processes are delicate, rather short and finely divided.

b. Wandering stage. The microglia cells are mobilized in trauma and other destructive lesions; their processes are withdrawn, the cells as a whole swell, become ameboid and ingest débris and fat droplets liberated during degeneration of the myelin.

C. Origin. The astroglia and oligodendroglia are ectodermic and arise within the embryonic neural tube from the ependymal layer (p. 155). The microglia is of mesodermic origin; it enters the central nervous system long before birth.

PART THREE: THE ORGANS

THE BLOOD VASCULAR SYSTEM

The tubular portions of the system (arteries, veins and capillaries) as well as the heart have a common and continuous lining of endothelium. In the thinnest vessels (capillaries) endothelium forms the entire wall. As the vessels become larger two more layers are added, namely: a middle muscular coat and an outer layer of fibrous connective tissue. The same three layers are found in the heart, in which the muscular coat is the most developed.

I. The Blood Vessels

A. Capillaries. Their diameter varies between 7 and 10μ. They form extensive networks whose meshes vary in size in the different organs.

1. Endothelium. The endothelial cells are arranged with their long axes parallel with the axis of the capillary. They have wavy outlines, seen only in silvered preparations.

2. Pericapillary cells. In addition to the fibroblasts and histiocytes of the surrounding tissue there are branched cells enveloping the endothelial tube (Rouget cells or pericytes) thought by some to be contractile. This, however, has not been proved for the mammal.

B. Arteries. Their diameter varies from tubes slightly larger than the capillaries (precapillary arterioles) to the large arteries visible in the gross.

1. Structure of the wall. Three layers are recognized:

a. Intima. Formed by endothelium, a subendothelial layer of delicate connective tissue and an elastic (fenestrated) plate: the inner elastic membrane.

b. Media. This is the muscle coat, composed of circularly arranged smooth muscle fibers with varying amounts of elastic and collagen fibers.

c. Externa or adventitia. Consists of connective tissue bundles mainly parallel with the axis of the artery.

2. Arterioles and small arteries. The transition between the capillaries and the small arteries is gradual.

a. Precapillary arterioles. Endothelial tubes with scattered, circularly arranged, smooth muscle fibers.

b. Arterioles. Similar to the preceding but with a continuous layer of smooth muscle fibers and an externa of collagenous fibrils. In the larger arterioles there is a delicate inner elastic membrane.

c. Small arteries. The media consists of two or more layers of circular muscle fibers. Elastic fibers also occur in this layer, as well as in the inner portion of the externa.

3. Medium-sized arteries. These include most of the arteries readily visible in dissections except the very large ones. Smooth muscle still predominates in their walls (muscular arteries).

a. Intima. Composed of endothelium, a subendothelial layer of delicate connective tissue and a well-developed inner elastic membrane. In cross sections the latter appears as a wavy line due to longitudinal folding. The intima may contain longitudinal smooth muscle fibers.

b. Media. The muscle fibers form from 20 to 40 circular layers. The elastic fibers are mostly circular but radially arranged elastic fibers may also occur. Argyrophil fibers are also present.

c. Externa. May be as thick as the media. The elastic fibers next to the media form coarse networks, and even an outer elastic membrane. Bundles of longitudinal smooth muscle fibers sometimes occur (splenic artery, dorsalis penis, ovarian arteries).

4. Large arteries. The elastic component predominates over the muscle, hence their yellowish color. They have relatively thin walls for their size. The aorta is the most typical.

a. Intima. The well-developed subendothelial layer contains

delicate longitudinal networks of elastic fibers. Inner elastic membrane composed of several fenestrated plates.

b. Media. Its main characteristic is the presence of numerous anastomosing, elastic fenestrated membranes which are arranged spirally. Between them there are thin collagenous bundles, argyrophil networks, fine elastic networks and the smooth muscle fibers. The latter have processes attached to the membranes; they form spirally arranged bands.

c. Externa. Is relatively thin and formed by collagenous bundles disposed in longitudinal spirals.

C. Veins. Their walls are thinner than those of the arteries due to a marked reduction of the muscular and elastic elements; this explains their collapse when not filled with blood.

1. Structure of the wall. It has the three layers present in the arteries but their boundaries are often indistinct because of the absence of definite limiting elastic membranes.

2. Venules and small veins. The transition between the capillaries and veins is effected through venous capillaries, post-capillary veins and venules, all of which have endothelium and an outer thin sheath of fibrous connective tissue.

a. Muscle fibers appear as scattered elements, which increase in numbers as the veins become larger.

b. Delicate elastic fibers also make their appearance.

c. A poorly defined inner elastic membrane may be present.

3. Medium-sized veins. These include all the veins readily seen in dissections except the main trunks (superior and inferior vena cava, innominates, portal vein, etc.).

a. Intima. This is always thin. A subendothelial layer is present in the larger veins. The inner elastic membrane is often indistinct. Longitudinal smooth muscle fibers may occur.

b. Media. Markedly reduced in thickness as compared with the media of the arteries. Contains circularly arranged smooth muscle cells separated by collagenous and elastic fibers. It is best developed in the veins of the leg.

c. Externa. This is the thickest layer of the vein. Besides collagenous and elastic fibers it has bundles of longitudinal smooth muscle fibers placed next to the media. In some veins these bundles form a continuous layer (suprarenal veins).

4. Large veins. The reduction in the amount of muscle in the

media reaches a maximum in the large veins, with a corresponding increase in the longitudinal muscle of the externa.

a. Intima. Very thin; it may have a distinct inner elastic membrane.

b. Media. Smooth muscle formed by scattered fibers separated by collagenous bundles and longitudinally and circularly arranged elastic fibers.

c. Externa. The longitudinal muscle bundles of the well-developed externa form a continuous layer, especially in some veins, i.e. the portal and the inferior vena cava.

5. Valves. Projections of the intima under the form of semilunar flaps with their concavity directed toward the heart are present in most veins, particularly in the lower extremity.

a. Their rôle is to prevent the back-flow of the blood.

b. They consist of connective tissue covered with endothelium, and contain fine elastic fibers.

D. Arterio-venous anastomoses. They are direct communications between small arteries and veins. When open, they shunt a considerable amount of blood directly into the veins, thus decreasing the flow through adjacent arterioles leading to the capillary bed.

1. Distribution. They abound in the skin of the palm of the hand, nail bed, nose, eyelids, etc.

2. Structure. Simple arterio-venous anastomoses have a relatively thick muscle wall. In other cases (glomus type) they are twisted and have modified muscle elements resembling epithelioid cells. The coccygeal body (glomus coccygeum) belongs to this type.

E. Vasa vasorum. These are small nutrient vessels which occur in the walls of arteries and veins. They arise from adjacent small arteries and ramify in the externa. They terminate in a capillary network which enters the media. In the veins they are more abundant and may reach the intima.

F. Nerves. The (vasomotor) supply is rich and consists mostly of axons from the sympathetic ganglia; they branch in the externa where they form plexuses from which twigs are given off to the media. Myelinated sensory fibers also occur.

II. The Heart

The three layers of the heart are: the endocardium, the myocardium and the epicardium. The first is continuous with the intima

of the large vessels connected with the heart; the myocardium or muscular coat corresponds to the media, and the epicardium to the externa, except that its outer surface is lined by the mesothelium of the visceral layer of the pericardium.

A. Endocardium. It is thinner in the ventricles than in the atria and auricles.

1. **Endothelium.** Consists of irregular polygonal cells.
2. **Subendothelial layer.** This is a thin layer of connective tissue.
3. **Fibro-muscular layer.** Fibrous connective tissue with an abundance of elastic fibers and scattered smooth muscle fibers.
4. **Subendocardial layer.** Loose connective tissue; serves as attachment to the myocardium. Absent from the papillary muscles and chordae tendinae. It contains branches of the conductive system (p. 39).

B. Myocardium. This is the thickest of the three layers and consists of the cardiac variety of striated muscle (p. 23). It is thinnest in the atria and thickest in the left ventricle.

1. **Atrial myocardium.** Two layers are recognizable:
   a. **Outer layer.** Common to both atria, with fibers running in a transverse or somewhat oblique direction.
   b. **Inner layer.** Independent for each atrium, with longitudinally arranged fibers forming bundles which stand out as ridges along the inside of the atria (pectinate muscles).
2. **Ventricular myocardium.** The arrangement of the layers is much more complicated and is best seen in dissections.
3. **Annuli fibrosi.** They surround the atrio-ventricular orifices and completely separate the atrial from the ventricular musculature. Composed of dense fibrous connective tissue.

C. Epicardium. Consists of three layers:

1. **Mesothelial layer.** Composed of flat, polygonal cells.
2. **Fibrous layer.** This contains flat networks of elastic fibers and numerous collagenous bundles.
3. **Subepicardial layer.** Loose connective tissue with variable amounts of fat. Here are placed the branches of the coronary vessels, nerve trunks and lymphatics.

D. Valves. The cardiac valves are folds of the endocardium.

1. **Atrio-ventricular valves.** They are attached to the annuli fibrosi and consist of a peculiar variety of fibrous connective tissue with

elastic networks and scattered smooth muscle fibers on the atrial surface of the valve. Both surfaces of the valve are lined with endothelium which also envelops the chordae tendinae, attached to the ventricular surface and margin of each valve.

2. **Aortic and pulmonary valves.** Their structure is similar to the above, but they do not have smooth muscle fibers.

E. The impulse-conducting system. Composed of peculiar muscle fibers which regulate the proper sequence of contractions of atria and ventricles.

1. **Structure.** The fibers of the system are rich in sarcoplasm and poor in myofibrils. The sarcoplasm contains abundant glycogen. Their size varies according to the location.

a. **Sino-atrial and atrio-ventricular nodes.** They consist of a network of thin, repeatedly anastomosed fibers whose meshes are filled with connective tissue.

b. **Atrio-ventricular bundle (of His).** This is sheathed by connective tissue. It consists of strands of anastomosed swollen fibers (Purkinje fibers) best developed in the calf, sheep, etc. The myofibrils are irregularly arranged.

2. **Termination.** The fibers of the conductive system terminate by connecting with the ordinary myocardial fibers, in the atria as well as in the ventricles. The connection is effected in the subendocardial layer.

F. Blood vessels, lymphatics and nerves. The heart is supplied with blood by the two coronary arteries. The arterial branches enter the myocardium where they form a rich capillary bed with elongated meshes.

1. **Lymphatics** are present in large numbers throughout the heart and they reach the endocardium.

2. There is a double nerve supply: sympathetic and parasympathetic. The fibers merge into an elaborate plexus at the base of the organ (deep cardiac plexus); this plexus contains ganglia of various sizes.

THE LYMPHATIC SYSTEM

The lymphatic system is composed of vessels (lymphatics) and organs (lymph nodes, tonsils, thymus, spleen). The organs consist of 'lymphoid' tissue, i.e. a reticulo-endothelial framework with its

meshes occupied by lymphocytes and histiocytes. They are located along the course of the lymphatics and contribute lymphocytes to the lymph passing through them. Diffuse lymphoid tissue occurs in many parts of the body, especially in the gastro-intestinal and respiratory tracts.

I. Lymphatic Vessels

They vary in size; their walls are thinner than those of the veins. They collect tissue juice (lymph) which is finally conveyed into the right lymphatic duct and the thoracic duct, respectively.

A. Capillaries. Formed by endothelium but instead of being cylindrical they have irregular constrictions and dilatations, and end blindly.

B. Lymphatics. The medium-sized lymphatics have walls with three layers which correspond to those in the walls of the veins, but their boundaries are indistinct. The thoracic duct has a muscular media thicker than a vein of the same size.

C. Valves. They occur in pairs placed on the opposite sides of the vessel. Their concave surfaces point in the direction of the lymph flow.

II. Lymph Nodes

They are located in the course of the lymphatics and serve as filters for the lymph before the latter reaches the main lymphatic ducts. They are more or less constantly found in certain regions of the body.

A. Shape. Lymph nodes are usually oval or elliptical and show an indentation, the hilus, where the blood vessels enter and leave the node. The efferent lymphatic or lymphatics leave the node through the hilus, while the afferent (i.e. the lymphatics bringing lymph into the node) enter at various points.

B. Size. It varies considerably (from 1 to 25 mm. in length).

C. Structure. A lymph node is enclosed within a connective tissue capsule. Two distinct areas are recognizable: an outer, dense, the cortex, and an inner, lighter, the medulla.

1. **Capsule.** Of variable thickness, it blends with the surrounding connective tissue. Smooth muscle fibers occur occasionally.
2. **Reticulum.** The capsule sends partitions (trabeculae) into the node, dividing the cortex into irregular compartments. The collagenous fibers of the trabeculae are continuous with the argyro-

phil fibers of the reticulum, which extends throughout the node but varies in density in different parts.

3. Cortex. The density of the cortex is due to the great abundance of cell elements occupying the meshes of the reticulum. A definite arrangement is present.

a. Nodules. In the cortical compartments there are roundish masses of closely packed lymphocytes, the nodules. They frequently contain lighter-staining central areas called germinal centers because they are the source of lymphocytes. The latter, however, arise also in other parts of the node. The nodules are temporary structures, i.e. they may disappear.

b. Cortical sinuses. The nodules are separated from the capsule and trabeculae by spaces (sinuses) through which the lymph circulates. The space between the cortex and the capsule is known as the peripheral or sub-capsular sinus and the afferent lymphatics open into it.

c. Transition with the medulla. The cortex is not sharply separated from the medulla but gradually merges with it.

4. Medulla. The trabeculae are irregularly arranged and anastomosed with each other.

a. Lymph or medullary cords. The lymphocytes do not form round masses but appear as a meshwork of strands separated from each other by sinuses.

b. Medullary sinuses. They are wide, irregular and frequently anastomosed. The reticulum extends through them, thus favoring phagocytosis of degenerated cells, foreign matter, bacteria, etc., suspended in the lymph. Phagocytosis is carried out by the numerous histiocytes of the reticulum.

c. Efferent lymphatics. The merging sinuses finally open into the efferent lymphatics through which the filtered lymph flows out of the node.

III. The Tonsils

The tonsils are lymphatic organs which constitute a protective ring at the gateway to the alimentary and respiratory tracts. They do not filter the lymph, but they are surrounded by plexuses of lymph capillaries which gradually merge into larger lymphatics. They produce numerous lymphocytes; those found in the saliva are known as salivary corpuscles.

A. Palatine (faucial) tonsils. They are partially covered by the buccal epithelium which also lines deep pockets (crypts) within the tonsil.

1. **Epithelium.** The epithelium is stratified squamous.
2. **Crypts.** They are deep, irregular depressions (10 to 20 for each tonsil). Their epithelial lining is usually infiltrated with lymphocytes.
3. **Lymph nodules.** Under the epithelium there is a mass of lymphoid tissue containing numerous lymph nodules. Germinal centers are present.
4. **Capsule.** The connective tissue capsule sends septa which separate the various crypts with their surrounding zones of lymphoid tissue.

B. Lingual tonsils. Occur in the dorsum and sides of the posterior part of the tongue. Their structure is similar to that of the palatine tonsils, but they have fewer crypts.

C. Pharyngeal tonsil. This is a median aggregation of lymphoid tissue in the posterior wall of the nasopharynx; it shows numerous folds but no crypts. The epithelium is pseudostratified ciliated (p. 7). Its hypertrophy in children constitutes what are known as adenoids.

IV. The Thymus

The thymus is an important lymphatic organ of childhood. It is gradually replaced by fat and connective tissue until in old age very little thymic tissue is left.

A. Structure. It is formed of two closely placed lobes each of which is surrounded by a connective tissue capsule which gives off numerous trabeculae; the latter subdivide the lobe into many lobules. Two parts are present in each lobule:

1. **Cortex.** It consists of densely packed small lymphocytes. Scattered among them are reticular cells with pale nuclei and indistinct outlines. Lymph nodules and germinal centers are absent.
2. **Medulla.** The transition between cortex and medulla is gradual. The medulla contains fewer lymphocytes.
   a. **Reticulum.** Although also present in the cortex it is more conspicuous in the less dense medullary region. Most of its cells are of endodermic origin (p. 124) but mesenchymal reticular cells also occur. Argyrophil fibers are found chiefly around the blood vessels.

b. Thymic (Hassall) corpuscles. Highly characteristic of the thymus. They are bodies (30 to 100μ or more) composed of concentrically arranged cells with acidophilic reaction. The cells show evidences of hyalinization and degeneration. In the center they may completely degenerate, the whole structure thus resembling a cyst.

B. Involution. The involution or regression of the thymus begins at puberty. The cortex becomes thinner through loss of the lymphoid cells. This is followed by degeneration of the medulla. The Hassall corpuscles are the last to disappear; a few may still be present in old subjects.

C. Lymphatics. Although the thymus is a lymphatic organ it does not contain lymph sinuses. The lymphatics begin around the lymphoid tissue of the lobules and fuse to form larger vessels.

V. The Spleen

The spleen lacks afferent lymphatics and lymph sinuses. It acts as a filter for the blood through the phagocytic activity of its histiocytes. It is also the source of numerous lymphocytes.

A. Structure. Except at the hilus the spleen is covered by the peritoneum, represented by a layer of mesothelium. Under this there is a capsule.

1. Capsule and trabeculae. The capsule and the trabeculae it sends into the organ are made up of dense connective tissue with scattered smooth muscle fibers. Elastic fibers also occur, specially in the trabeculae.

2. Lobules. The trabeculae arising from the capsule divide the organ into numerous more or less distinct lobules.

3. Splenic pulp. The spaces between the trabeculae are filled with a soft tissue known as the splenic pulp. Two varieties are recognizable:

a. White pulp. Consists of lymphoid tissue which forms a sheath about the arteries.

(1) Splenic corpuscles (Malpighian bodies). The sheath enveloping the arterial branches has spherical or elliptical enlargements, the splenic corpuscles, seen in the gross. They are really lymph nodules and may have germinal centers.

(2) Stroma. The stroma is a network of argyrophil fibers, the meshes of which are packed with lymphocytes.

b. Red pulp. It is traversed everywhere by a plexus of venous sinuses which break it up into anastomosing cords (pulp cords) similar to those in the medulla of the lymph nodes. The red color is due to the blood in the sinuses.

(1) Stroma. A framework of argyrophil fibers continuous with those of the white pulp and with the collagenous bundles of the trabeculae. This reticulum has fixed histiocytes and mesenchyme cells.

(2) Cell elements. In the meshes of this framework there are lymphocytes, free histiocytes (splenocytes) and all the elements of the circulating blood.

(a) Monocytes are very numerous; according to some authors they are formed in large numbers in the spleen.

(b) Megakaryocytes occur in the spleens of infants and of some animals (cat, dog, rat).

B. Blood supply. Since the spleen acts as a filter for the blood its blood vessels show a definite arrangement to carry out this function.

1. Arteries. The branches of the splenic artery enter the hilus and pass along the trabeculae, branching repeatedly until they become quite small.

a. Central arteries. The smaller arterial branches leave the trabeculae, enter the lobule and become sheathed by the white pulp. Since sometimes the artery is seen near the center of a splenic corpuscle it is termed 'central artery.'

b. Penicilli. When the central arteries attain a diameter of 40 to 50μ they leave the white pulp and enter the red pulp, where each branches into a tuft of small, straight vessels, resembling a brush (penicillus). Each branch of the penicillus shows three parts:

(1) Pulp arteries. They are the longest of the three divisions and possess a muscular media. They become smaller and divide into the:

(2) Sheathed arteries, which have an unusually thick wall for their size. The sheath (of Schweigger-Seidel) is of reticular nature and is not so well developed in man as in animals (pig, dog). Muscle fibers are absent.

(3) Terminal portions. Each sheathed artery divides into two or three branches which represent simple arterial capillaries.

2. Veins. They begin in the red pulp as venous sinuses, so called

because of their wide irregular lumen. Between the sinuses are the pulp cords.

a. **Venous sinuses.** Their walls are not lined by ordinary endothelium. Instead there are long, narrow cells parallel with the axis of the vessel; they are fixed histiocytes, though not intensely phagocytic.

(1) The walls of the sinuses are supported by circularly arranged argyrophil fibers, and some authors claim that they have numerous openings through which cells may pass.

b. **Pulp veins.** Arise through fusion of the venous sinuses.

c. **Trabecular veins.** The pulp veins coalesce to form the trabecular veins, which ultimately form the splenic veins leaving the organ at the hilus.

3. **Union of the arteries and the veins.** The mode of termination of the arterial capillaries (the third section of the branches of the penicilli) is a matter of controversy.

a. Some authors think that they open into the intercellular spaces of the red pulp (open circulation).

b. Others believe that all the arterial capillaries connect directly with the venous sinuses (closed circulation).

c. According to a third view some of the capillaries open into the intercellular spaces while others connect directly with the sinuses.

d. Observations in the living favor the second view.

THE INTEGUMENT

The integument comprises the skin and its derivatives (cutaneous glands, hair, nails).

I. The Skin

It consists of two main layers: the surface epithelium or epidermis and the underlying dense connective tissue layer, the derma or corium. Beneath the latter there is a layer of loose connective tissue, the subcutaneous layer which attaches the skin to the deeper tissues. In certain parts this layer is rich in adipose tissue (panniculus adiposus).

A. **Epidermis.** Is a stratified squamous epithelium the external layer of which undergoes cornification and thus protects the skin against

drying. The boundary line between the epidermis and derma is very wavy; this is due to the presence of projections of the derma (dermal papillae) which are seldom absent.

1. Thickness. It varies according to the region of the body. It is thickest in the palms of the hands and soles of the feet where its structure is most typical.

2. Structure. The following layers can be distinguished:

a. Malpighian layer (stratum germinativum). This is the deepest of the layers. It is thicker between the dermal papillae than above them. Two sublayers may be mentioned:

(1) Basal layer (stratum cylindricum). Composed of a single row of columnar cells with indistinct outlines. Mitotic figures occur rather frequently. It rests on the well-developed basement membrane and gives rise to the layers above it.

(2) Spiny layer (stratum spinosum). The cells are polyhedral except near the upper surface where they are more flattened. They are connected with each other by intercellular bridges which appear as spines in isolated cells, hence the name given to this sublayer.

b. Granular layer (stratum granulosum). It consists of flattened cells whose cytoplasm contains irregular granules of keratohyalin which eventually cause disintegration and fading of the nucleus. The intercellular spaces become narrower. May be absent where the epidermis is very thin.

c. Stratum lucidum. Consists of closely packed, flattened cells with no visible nuclei. The keratohyalin granules have dissolved and become eleidin. Absent in thin epidermis.

d. Horny layer (stratum corneum). Composed of dead, cornified cells without nuclei, and cytoplasm filled with keratin. It is thickest in the palms and soles. The most peripheral layers appear as dried, horny scales which are continuously cast off (stratum disjunctum).

3. Pigmentation. The color of the human skin depends mainly on the presence of granules of melanin within the cells of the Malpighian layer, particularly in the basal sublayer. The granules gradually disappear as the deeper cells move toward the surface. In the Negro there is a greater amount of pigment in all layers of the epidermis.

B. Derma. The thickness of the derma roughly corresponds to that

of the epidermis. It consists of fibrous connective tissue with abundant, thick elastic networks, some of which are inserted on the basement membrane of the epidermis.

1. **Papillary layer.** Occupies the dermal papillae and the portion immediately beneath the epidermis, and consists of loose connective tissue with numerous cells and fine networks of elastic fibers. It passes gradually into the:

2. **Reticular layer,** occupied by stout bundles of collagenous fibers which form a dense feltwork. The elastic fibers are correspondingly thick.

C. Subcutaneous layer (hypodermis). It is a continuation of the derma and is composed of loose connective tissue with variable numbers of fat cells. It is penetrated everywhere by large blood vessels and nerve trunks.

II. The Cutaneous Glands

The glands of the human skin include the sebaceous, sweat, and mammary glands. The latter will be described in the section dealing with the female genital system (p. 89).

A. Sebaceous glands. They produce an oily secretion (sebum) which lubricates the surface of the skin and prevents maceration when the latter is moistened. In some areas of the body they open directly on the surface of the skin, but in most cases their ducts empty the secretion into the upper portion of the hair follicles (p. 48).

1. **Secretory portions.** They are round sacs (alveoli) grouped together like a bunch of grapes and opening into a common secretory duct.

   a. **Structure.** The alveolar wall is formed by a basement membrane lined internally by a single layer of cells with round nucleus. The alveolus is filled with large, polygonal cells with their cytoplasm occupied by fat droplets (dissolved in routine sections).

   b. **Release of the secretion.** With the increase in size of the fat drops the nuclei become irregular in outline and finally shrink and disappear. The cells break down and the fat is liberated (holocrine type of secretion).

2. **Duct.** The duct is lined by stratified squamous epithelium con-

tinuous with the epidermis. Mitoses are numerous in the epithelium, the newly formed cells falling into the alveoli.

B. Sweat glands. The sweat or sudoriparous glands are simple, coiled tubes.

1. Secretory portion. This is the coiled part of the gland, which is usually located in the derma.

a. Basement membrane. The walls of the secretory portion have a thick basement membrane. Internal to the membrane are the:

b. Myo-epithelial cells. Flattened, spindle-shaped cells with their long axis approximately parallel to that of the glandular tube. They are contractile and arise from ectoderm (p. 155).

c. Glandular cells. They are cuboidal or low columnar with basal ends which fit into the spaces between the myo-epithelial cells. The nuclei are round. The cytoplasm may contain secretory granules and vacuoles, and sometimes fat droplets.

2. Duct. It is a thin, slightly twisted and curved tube, lined by a double-layered epithelium. Myo-epithelial cells are absent. It opens on the surface of the horny layer of the epidermis.

III. The Hair

Hairs are horny threads developed from the epidermis. They grow within deep narrow pits (hair follicles) sunken into the derma to varying depths. Each hair consists of a shaft which projects above the surface, and a root which occupies the hair follicle. The root is expanded below into the hair bulb.

A. Structure of the hair. It is composed entirely of epithelial cells arranged into three layers:

1. Medulla. Forms the core or axis of the hair. It consists of two or three layers of cuboidal cells. Their cytoplasm stains lightly and contains finely dispersed pigment and granules resembling eleidin. Absent in the lanugo (p. 154).

2. Cortex. It is formed of several layers of spindle-shaped cells with shrunken nuclei. Pigment is found in the cortex of colored hairs. The intercellular spaces contain air, as in the medulla.

3. Cuticle. Composed of a single layer of flat, non-nucleated cells which overlap each other like the scales of a fish.

B. Structure of the hair follicle. It consists of the inner and outer root sheaths (epidermal) and a connective tissue sheath (dermal). Sebaceous glands open into the upper portion of the hair follicle.

1. Inner root sheath. Composed of three distinct layers: the cuticle of the root sheath, and the layers of Huxley and Henle, respectively.

2. Outer root sheath. Is the direct continuation of the Malpighian layer of the epidermis, and, as in the latter, there is a row of columnar cells (stratum cylindricum).

3. Connective tissue sheath. Composed of circular and longitudinal connective tissue fibers. As the bulb is approached this layer disappears.

4. Hair bulb. This is a mass of growing epithelial cells (matrix) not arranged into layers. It causes the growth of the hair in length.

5. Hair papilla. The vascular connective tissue papilla which projects into the enlarged hair bulb.

6. The muscle of the hair (arrector pili). It is a band of smooth muscle fibers which arises from the papillary layer of the skin and is inserted in the connective tissue sheath about the middle of the follicle. When it contracts (from cold, etc.) it shifts the hair from a sloped to a vertical position. By pressing on the sebaceous gland it facilitates the discharge of its secretion.

IV. The Nails

The nails consist of closely welded, horny scales (cornified epithelial cells) arranged in layers. The skin under the nail is called the nail bed. Each nail is covered posteriorly by the nail fold, which has the structure of the skin.

A. Nail bed. The epithelium of the nail bed corresponds to the Malpighian layer of the skin.

1. The epithelial portion which lies beneath the root and the part corresponding to the lunula is thicker and is called the matrix because it is the growing portion of the nail.
2. In the derma there are arterio-venous anastomoses (p. 37).

B. Eponichium. This is the horny layer of the nail fold spreading over the upper surface of the nail root (the so-called 'cuticle').

C. Hyponichium. The epithelium of the nail bed becomes continuous with the Malpighian layers of the skin under the free edge of the nail; the thickened horny layer in this location is called the hyponichium.

V. Nerves

Although the nerves of the skin are mainly sensory they carry sympathetic fibers for the supply of the vessels, the arrectores pilorum and the myo-epithelial and secretory cells of the sweat glands. The sensory fibers terminate as intraepithelial endings in the epidermis (p. 28) or in special nerve endings. The location of the latter is the following:

A. In the derma. Tactile (Meissner) corpuscles (p. 29) occur in the papillae, especially in the finger tips, palm and sole. End bulbs (p. 29) are usually located in the papillary layer.

B. In the subcutaneous layer (hypodermis). There are Pacinian corpuscles (p. 29) as well as other special endings (Golgi-Mazzoni corpuscles of the finger tips; corpuscles of Ruffini).

THE DIGESTIVE SYSTEM

I. General Structural Plan

The walls of the digestive system, especially its tubular portions, are built under a general structural plan. Four coats or tunics are recognizable:

A. Mucosa. This is the innermost coat or mucous membrane consisting of:

1. **The lining epithelium,** of different type according to the region.
2. **The underlying tunica (or lamina) propria.** Connective tissue of variable density.
3. **The muscularis mucosae.** A thin layer of smooth muscle present in most parts of the digestive tube.

B. Submucosa. A layer of loose connective tissue which lies beneath the mucosa. It is rich in blood vessels, lymphatics and nerves.

C. Muscularis. Consists of smooth muscle fibers, typically arranged in two layers:

1. **The inner circular.**
2. **The outer longitudinal.**

D. Adventitia. Fibrous connective tissue blending with the surrounding structures in the upper (pharynx, oesophagus) and lower (rectum) regions of the tube. In those portions within the abdominal cavity (stomach, small and large intestine) it is replaced by a

thin layer of connective tissue and mesothelium (the visceral peritoneum) called the tunica serosa or serous coat.

II. The Mouth

The lining of the mouth cavity (oral mucosa) contains numerous salivary glands of various sizes.

A. Mucosa. It consists of stratified squamous epithelium lying upon a tunica propria. A muscularis mucosae is not present.

1. Epithelium. Its thickness varies in different parts of the mouth. The superficial cells appear somewhat swollen and retain their nuclei. An abrupt change occurs in the margin of the lips where the epithelium of the skin passes over into the thicker, noncornified oral epithelium.

2. Tunica propria. Is thrown into papillae and consists of loose connective tissue with abundant cells.

B. Submucosa. The boundary line between the tunica propria and the submucosa is indistinct. The latter consists of a firm connective tissue with few elastic fibers. The submucosa blends externally with the connective tissue (fascia) of the musculature of the mouth.

C. Glands. They are small, branched structures present everywhere except in the gums. They have a duct and secretory portions (alveoli or acini), the whole resembling a small bunch of grapes. They either produce a watery fluid (serous or albuminous glands) or a more viscid secretion (mucous glands). Mixed glands also occur. They all contribute to the formation of the saliva.

1. Serous (albuminous) glands. The alveoli are formed by columnar or high cuboidal cells which contain numerous secretion granules, the antecedents of an enzyme (ptyalin). The nucleus is round or oval and occupies the basal half of the cell. In routine slides (hematoxylin-eosin) the serous cells have a pinkish color.

2. Mucous glands. The cells are larger, have a vacuolated aspect and appear bluish in routine slides. The droplets of mucigen (the antecedent of mucin) are usually dissolved. In cells filled with mucus the nucleus is pressed against the base of the cell. When the secretion is extruded the cell collapses and the nucleus becomes round. The alveoli of mucous glands have a tendency to branch. The palatine glands belong to this type.

3. Mixed (sero-mucous) glands. The relative number of cells of the two types varies considerably. As a rule the mucous cells are

near the ducts; when they predominate the serous cells are pushed to the blind ends of the alveoli where they form crescents (demilunes of Gianuzzi). They may be so crowded that their free (secretory) ends do not seem to reach the lumen.

4. Ducts. They consist of a layer of columnar cells; more than one layer is present as the duct nears the epithelium.

III. The Salivary Glands

The larger salivary glands are distinct, lobulated organs consisting of secretory epithelium (parenchyma) and a connective tissue framework (stroma). The parotid and submaxillary are enclosed within a connective tissue capsule; the sublingual has no capsule. In man, the parotid has only serous alveoli; the submaxillary and sublingual are sero-mucous.

A. Parotid. Is the largest of the salivary glands.

1. Stroma. Septa which arise from the connective tissue capsule divide the gland into lobes and smaller units (lobules) occupied by the secretory alveoli. The latter are separated from each other by loose connective tissue rich in argyrophil fibers. Fat cells frequently occur in the stroma; they increase in number with age.

2. Alveoli. They are spherical and purely serous. Occasionally a few mucous alveoli occur. Peculiar branched cells (basket cells) located in the periphery of the alveoli, internal to the basement membrane, abound in the parotid. They have been regarded by some as myo-epithelial (contractile) cells.

3. Ducts. The duct system of the parotid is complex. The smallest ducts are known as:

a. Intercalated ducts. They arise from the alveoli and are composed of low, sometimes flat, epithelial cells. They are fairly long.

b. Secretory (salivary) ducts. Lined by a single layer of columnar cells; their basal portions have a characteristic striated appearance. The cells are believed to contribute water and calcium salts to the saliva. The secretory ducts are mainly intralobular.

c. Excretory (interlobular) ducts. They follow the connective tissue septa and join to form interlobar ducts. Their epithelium is simple columnar.

d. Main (Stenson's) duct. It opens into the mouth cavity. It is

lined with pseudostratified columnar epithelium with the nuclei appearing in two layers.

B. Submaxillary. The human submaxillary is preponderantly serous. In the dog and cat it closely resembles the sublingual.

1. Stroma. Similar to that of the parotid.

2. Alveoli. The serous alveoli are spherical, the mucous slightly branched. Mixed alveoli may also occur, with the serous component arranged in demilunes.

3. Ducts. Same as in the parotid but the intercalated ducts are short and narrow, and the secretory longer and more numerous.

C. Sublingual. It is the smallest of the salivary glands and in man is chiefly mucous.

1. Stroma. Similar to that of the preceding but a capsule is absent.

2. Alveoli. They are either purely mucous or mixed. The demilunes are large and numerous.

3. Ducts. The ducts of the sublingual are simpler than in the parotid and submaxillary. The intercalated ducts are rudimentary or even absent. The secretory portions, greatly reduced in number, are represented by groups of cells with basal striations in the walls of the excretory ducts.

IV. The Tongue

The tongue is a muscular organ covered by a mucous membrane. It is abundantly supplied with vessels and nerves.

A. Mucosa. It lacks a muscularis mucosae.

1. Epithelium. Stratified squamous. In the upper surface of the tongue it forms projections visible with the naked eye, known as the lingual papillae.

a. Filiform papillae. They are the most numerous and occur over the entire dorsum of the tongue. Each consists of a long, slender connective tissue papilla covered by epithelium which forms secondary pointed projections. The most superficial epithelial cells are keratinized.

b. Fungiform papillae. So-called because each resembles somewhat a mushroom. They are scattered irregularly among the filiform but they are less numerous. The connective tissue which forms the core is more or less studded with secondary papillae. The superficial layer of the epithelium is not cornified.

c. Circumvallate (vallate) papillae. They are the largest; there

are from 9 to 15 in number, and are strewn along a V-shaped line on the posterior surface of the dorsum of the tongue. Each rises from the bottom of a deep, circular depression. The epithelium is not cornified and contains taste buds; these will be considered later (p. 95).

d. Foliate papillae. In some animals (rabbit) they are parallel folds arranged like the pages (or folios) of a book, but in man they are rudimentary. They are located on the lateral surface of the posterior part of the tongue and contain numerous taste buds.

2. Tunica propria. Composed of loose connective tissue with numerous cells; it forms the core of the papillae.

3. Glands. Connected with the circumvallate papillae there are well-developed serous glands (of von Ebner) which open at the bottom of the furrow around the papilla. Their bodies are deeply placed, among the musculature. Other glands (mucous or mixed) also occur.

B. Submucosa. It is absent in the dorsum, where the tunica propria blends with the connective tissue of the underlying muscle.

C. Stroma. Consists of fibrous connective tissue which separates the muscle fibers into bundles. In it are placed the bodies of the glands. Fat cells may be numerous. It also forms a vertical partition (septum linguae) which divides the tongue into right and left halves.

D. Musculature. This is very complex and consists of striated muscle fibers which are often branched at their ends. They are oriented in every direction, but three fairly distinct planes—vertical, transverse and longitudinal—can be differentiated.

E. Nerves. The tongue is supplied by four of the cranial nerves: the trigeminus, facial (through the chorda tympani), glossopharyngeal and hypoglossus. The first three carry sensory fibers, while the last named is the motor nerve.

1. The facial and glossopharyngeal carry the fibers for taste.
2. Ordinary sensation is transmitted through the glossopharyngeal and the lingual branch of the trigeminus.
3. Small (parasympathetic) ganglia occur in the tongue, specially in the posterior region.
4. Sympathetic (vasomotor) fibers are also present.

V. The Teeth

A tooth consists of a crown, projecting above the gum, and a root or roots imbedded in the dental alveolus. The bulk of the tooth is composed of dentine which in the crown is covered by the enamel and in the root by the cementum. The tooth is hollow. Its central cavity (pulp chamber) is occupied by a soft connective tissue (dental pulp); the cavity extends throughout the root as the root canal.

A. Enamel. It is the hardest substance of the body, and it is mostly inorganic matter. It is made up of very slender rod-like columns (enamel prisms) cemented together; the prisms are grouped into bundles, but the latter are not parallel. It is thickest over the crown and gradually decreases in thickness until the neck of the tooth is reached, where it stops.

B. Dentine. It is somewhat harder than bone, but it differs from the latter in that it lacks cells, although it contains canaliculae (dentinal canals). Blood vessels are absent.

1. **Dentinal canals.** They begin at the dental pulp and pass outward radially. They are more or less parallel, but they describe an S-shaped curve and, in addition, they are twisted spirally. The canals give off minute branches which anastomose with similar branches from other canals. They contain prolongations of the odontoblasts (see below).
2. **Ground substance.** This occupies the spaces between the dentinal canals and contains systems of very thin collagenous fibrils arranged in bundles; their general direction is parallel to the long axis of the tooth (i.e. perpendicular to the dentinal canals). They correspond to the fine collagenous fibrils of the bone matrix (p. 16). The ground substance is calcified.

C. Cementum. Like bone tissue it contains lacunae and osteocytes, which are irregularly distributed and may not occur in considerable areas. Canaliculae radiating from the lacunae are also present. Sharpey fibers (p. 17) enter the cementum, which is non-vascular.

D. Peridental (periodontal) membrane. Is a layer of dense fibrous connective tissue which surrounds the root of the tooth and fills the space between it and the alveolus. It serves to attach the tooth to the walls of the alveolus.

E. Dental pulp. Fills the pulp cavity. It contains the odontoblasts and an embryonic or poorly differentiated form of connective tissue.

1. **Odontoblasts.** They produce the dentine and are arranged in a layer in the periphery of the pulp. They are tall, rather basophilic, and oriented radially. One or more processes (Tomes fibers) enter the dentinal canals. The odontoblasts are comparable with the osteoblasts.

2. **Pulp tissue.** It contains numerous thin collagenous fibrils which are not combined into bundles, but run in every direction. The fibroblasts are branched more or less profusely, and the ground substance is gelatinous and slightly basophilic.

VI. The Pharynx

The pharynx is the meeting point of the respiratory and digestive passages. The character of the mucosa differs according to the region and is subject to individual variations. Its wall consists of three layers:

A. **Mucosa.** It has an epithelium and a tunica propria. The former is stratified squamous, but toward the naso-pharynx it may be pseudostratified ciliated. Mucous and mixed glands are present.

B. **Muscularis.** Since there is no muscularis mucosae and the submucosa is poorly developed the muscularis is very close to the mucosa. It contains irregularly arranged striated muscle fibers which belong to the constrictors of the pharynx.

C. **Fibrous layer.** This is a dense network of collagenous and elastic fibers, which binds the pharynx to the surrounding structures.

VII. The Oesophagus

The walls of the oesophagus have the four layers characteristic of the tubular portions of the digestive tract.

A. **Mucosa.** The inner surface of the oesophagus is thrown into longitudinal folds.

1. **Epithelium.** Stratified squamous throughout; it ends abruptly at the cardia of the stomach. It is not cornified.

2. **Tunica propria.** Loose connective tissue, rather cellular. Contains the cardiac (superficial) glands (see E).

3. **Muscularis mucosae.** This is well developed and consists of closely placed but independent bundles of smooth muscle fibers longitudinally arranged. It increases in thickness in the lower third of the oesophagus.

B. **Submucosa.** It has thick collagenous and elastic networks, and

contains the larger blood vessels, lymphatics and nerves, as well as the bodies of the irregularly distributed mucous glands (see E). It penetrates into the folds of the mucosa.

C. Muscularis. Its character varies according to the level. In the upper third it is formed by striated fibers; in the middle, there are striated and smooth muscle fibers, in the lower third only smooth fibers arranged in two distinct layers, inner circular and outer longitudinal. In the upper third the arrangement of the muscle is more irregular.

D. Adventitia. Consists of bundles of collagenous fibers with many elastic fibers. It blends with the mediastinal connective tissue. In it are placed the larger vessels and nerve trunks.

E. Glands. The oesophagus has two kinds of glands:

1. **Mucous (oesophageal) glands.** They are irregularly scattered and resemble the glands of the buccal mucosa, but, with few exceptions, they are entirely mucous. The alveoli lie in the submucosa. The main duct widens into an ampulla before it crosses the muscularis mucosae.
2. **Cardiac (superficial) glands.** They are branched glands contained within the tunica propria; their epithelial lining closely resembles that of the cardiac portion of the stomach (p. 59). They are chiefly found in the upper and lower thirds of the oesophagus.

F. Nerve plexuses. In the middle and lower thirds of the oesophagus the branches of the vagus give rise to two nerve plexuses which occur also in the stomach and intestine.

1. **Superficial plexus.** It has swellings occupied by small (parasympathetic) ganglion cells. The ganglia and plexus occupy the connective tissue which separates the inner (circular) and outer (longitudinal) muscle layers. Preganglionics end in the ganglia.
2. **Deep plexus.** The ganglia are smaller and fewer in number than in the superficial plexus. They are located in the submucosa.

VIII. The Stomach

The inner lining of the empty stomach is thrown into irregular, mostly longitudinal folds. The four characteristic coats are present, but the muscularis contains more than two layers of smooth muscle fibers, and the adventitia is replaced by a serous layer.

A. Mucosa. The mucosa shows a very large number of minute de-

pressions—the gastric pits—which are the openings of the gastric glands. The secretory portions of the latter are imbedded in the tunica propria.

1. **Epithelium.** The ridges between the gastric pits and the walls of the latter are lined by simple columnar epithelium composed of mucus-secreting cells. It begins abruptly at the cardia and ends at the pylorus.

2. **Glands.** Simple, or branched tubules, perpendicular to the surface. There are three main kinds: fundus or peptic, pyloric, and cardiac. The first are distributed through the greater part of the mucosa, while the other two are confined to the regions of the pylorus and cardia, respectively.

a. **Fundus (peptic) glands.** Simple, sometimes slightly branched, tubular glands several of which (3 to 7) open into each gastric pit. Each tubule consists of a mouth opening into the pit, a neck, a body and a slightly dilated blind end or fundus. The following types of cells occur:

(1) Chief (zymogenic) cells. They are arranged in a single layer which lines the lower half or third of the glandular tubule. They contain abundant pepsinogen granules, the antecedent of pepsin, but in routine slides the granules are dissolved and what remains are vacuoles separated by a delicate, bluish meshwork. The nucleus lies in the basal half of the cell.

(2) Parietal (oxynthic) cells. Oval or polygonal cells with spherical, centrally located nucleus. The cytoplasm is finely granular and acidophilic. They are most numerous in the upper half of the gland; in the lower half they are crowded by the chief cells and occupy a more peripheral position. They produce the antecedent of the hydrochloric acid present in the gastric juice.

(3) Mucous neck cells. They are found in the neck region of the gland. They have a pale cytoplasm in routine sections but when stained for mucus they are seen to contain many small granules, the antecedents of a secretion different from the mucus secreted by the gastric epithelium. The nuclei are usually flat, sometimes concave, and occupy the base of the cell.

b. **Pyloric glands.** The pits are deep and they occupy a much

greater proportion of the mucosa than the pits of the fundus glands. The glandular portions, branched and coiled, are lined with a single type of cell with pale cytoplasm. Parietal cells occasionally occur, especially in the area of transition from the fundic to the pyloric region.

c. Cardiac glands. The glandular portions open directly into the pits and are lined with clear cells similar to the elements of the pyloric glands. The transition between the region of the cardia and the fundus is not abrupt.

3. Tunica propria. It fills the spaces between the glands, and consists of connective tissue rich in argyrophil fibers. Numerous cells occur (fibrocytes, lymphocytes and plasma cells, eosinophilic leucocytes). Spherical masses of lymphoid tissue occur, especially in the pyloric region.

4. Muscularis mucosae. Consists of an inner circular and an outer longitudinal layer of smooth muscle; in some places there is a third outer circular layer.

B. Submucosa. Loose connective tissue which contains fat cells, lymphocytes and eosinophilic leucocytes. The large blood and lymph vessels are located here.

C. Muscularis. Three layers are present: outer longitudinal, middle circular and inner oblique. The middle layer is the most regular and continuous of the three. It forms the circular sphincter of the pylorus. In the fundus the separation of the three layers is often difficult.

D. Serous coat. Loose connective tissue covered with mesothelium; it continues into the large and small omentum.

E. Nerve plexuses. Similar to those of the oesophagus and in the same location.

IX. The Small Intestine

The mucosa of the small intestine is beset with very numerous outgrowths or villi which enormously increase its surface. The presence of permanent circular folds contributes to the same end. The folds are more numerous and best developed in the distal half of the duodenum and proximal part of the jejunum where they are known as the plicae circulares or Kerkring's valves.

A. Mucosa. It has a covering epithelium, a tunica propria largely occupied by the intestinal glands and a muscularis mucosae.

1. Epithelium. It consists of columnar (absorbent) cells and gob-

let cells. The latter are less numerous and occur interspersed with the columnar. The columnar cells vary somewhat in height; their free surface is covered by a striated border (or cuticle). Migrating lymphocytes often occur in the epithelium.

2. Villi. The shape of the villi varies according to the region (see below). Each villus is formed by a core of connective tissue enclosing a single lymphatic capillary. The whole is covered by epithelium, except at the base. The lymphatic (or lacteal) ends blindly near the tip of the villus. The connective tissue core has argyrophil fibrils, fibrocytes, lymphocytes and sometimes plasma cells. Smooth muscle fibers arranged longitudinally (i.e. parallel to the long axis of the villus) also occur; their contraction shortens the villus.

3. Glands. The glands (crypts of Lieberkühn) are simple tubular. Several cell types are present in them. Goblet cells also occur.

a. Columnar cells. They are similar to the absorbent cells but they lack a cuticular border. Some of them are seen in mitosis. Toward the bottom of the gland they are low columnar.

b. Paneth cells. They are restricted to the bottom of the glands. The distal half of the cell is filled with numerous, large acidophilic granules, the nature of which is not clear.

c. Argentaffine cells. They have specific (argyrophil) granules in their cytoplasm. They occur scattered singly among the other epithelial elements. Their function is obscure.

4. Tunica Propria. It fills the spaces between the crypts and between the blind ends of the latter and the muscularis mucosae. It is rich in argyrophil and elastic fibrils. The meshwork contains fibrocytes, histiocytes, lymphocytes, plasma cells and leucocytes. Small lymph nodules often occur. When they are aggregated they push downward through the muscularis mucosae and enter the submucosa. With further growth they protrude into the intestinal lumen (Peyer patches of the ileum).

5. Muscularis mucosae. Consists of two layers of smooth muscle: inner circular and outer longitudinal.

B. Submucosa. Loose connective tissue; it contains the larger blood vessels and lymphatics, also a ganglionated nerve plexus (of Meissner). In the upper duodenum it is occupied by the duodenal (Brunner) glands (see below). In the lower duodenum and the jejunum it enters the plicae circulares.

C. Muscularis. Consists of two well-defined layers of smooth muscle, an inner circular and an outer longitudinal. In the connective tissue that separates the two layers there is a ganglionated (parasympathetic) plexus (myenteric or Auerbach plexus).

D. Serous coat. Similar to that of the stomach; it is continuous with the mesenteries.

E. Regional differences. Although the structure just described applies in general to the small intestine there are some differences in its three divisions.

1. **Duodenum.**
   - **a. Villi.** They are wide, leaf-like structures disposed transversely, i.e. at right angles to the axis of the intestine.
   - **b. Duodenal (Brunner) glands.** Located in the submucosa of the upper portion of the duodenum. They are profusely branched and have wide lumina. Their cells closely resemble mucous cells; the nuclei, placed at the base, are usually flattened. The ducts open into the crypts of Lieberkühn.
2. **Jejunum.** The plicae circulares are tall, narrow folds formed by the submucosa. They are beset with numerous villi; solitary lymph nodules may occur in them. The folds become lower and more scattered toward the ileum.
3. **Ileum.** The folds of the ileum are very low and widely scattered. The villi are finger-like. Aggregated lymph nodules and the large, pear-shaped Peyer patches occur in the distal half of the ileum. The protruding portion of each patch is covered by epithelium with but a few, poorly developed villi.

X. The Large Intestine and Vermiform Appendix

The most important histological difference between the small and large intestine is the absence of villi in the latter. The mucosa is not thrown into folds except in its last portion, the rectum, in which longitudinal folds (rectal columns) occur.

A. Large intestine.

1. **Mucosa.**
   - **a. Epithelium.** The same cell types as in the small intestine.
   - **b. Glands.** The crypts of Lieberkühn are deeper than in the small intestine. Goblet cells are very numerous. Paneth cells are normally absent.

c. Tunica propria. Contains many lymphocytes and solitary lymph nodules; the latter extend into the submucosa.

d. Muscularis mucosae. Consists of inner circular and outer longitudinal smooth muscle fibers.

2. Submucosa. As in the small intestine; it may contain abundant fat cells.

3. Muscularis. The inner circular layer is well developed. The outer longitudinal is massed into three thick bands, the taenia (lineae) coli. Between the latter the longitudinal muscle layer is thinned. It becomes a uniform layer in the rectum. The myenteric plexus is present between the layers.

4. Serous coat. It forms the appendices epiploicae which consist chiefly of adipose tissue. Absent in the lower part of the rectum.

B. The appendix. The lumen in many adults is nearly or completely obliterated, or the mucosa and submucosa may be replaced by fibrous connective tissue (fibrous appendix).

1. Mucosa. Similar to the mucosa of the large intestine. The tunica propria is heavily infiltrated with lymphocytes and contains solitary lymph nodes which may form a complete ring. The larger follicles push through the muscularis mucosae and enter the submucosa. Argentaffine cells are common in the crypts.

2. Submucosa. It often contains numerous fat cells.

3. Muscularis. The inner circular layer is well developed. The outer longitudinal is of uniform thickness. The myenteric plexus is prominent and contains numerous ganglia.

4. Serous coat. As in the large intestine, but lacks appendices epiploicae.

XI. The Pancreas

The pancreas is a large, compound tubulo-acinar gland. It consists of an exocrine portion which produces the pancreatic juice, and an endocrine portion. The latter is represented by cell aggregations scattered throughout the organ, the islands of Langerhans. Their secretion (insulin) plays an essential rôle in the regulation of carbohydrate metabolism.

A. Stroma. The pancreas is covered by a thin connective tissue layer from which septa pass into the gland, subdividing it into lobules. In the lobules it forms a framework rich in argyrophil fibers.

B. Exocrine portion. This is represented by spherical or somewhat elongated acini connected with ducts.

1. Acini. They are lined with a single row of pyramidal epithelial cells resting on a basement membrane. The size of the lumen and the aspect of the cells vary with the activity of the organ.

a. Secretory cells. Their basal portion, containing the nucleus, is occupied by a basophilic, usually striated substance which stains bluish in routine slides. The distal portion appears pink; it contains numerous coarse zymogen granules, the antecedent of trypsin. The granules are seldom seen in routine slides.

b. Centro-acinar cells. They are seen in many acini. They are flat epithelial cells lying in contact with the apices of the secretory cells. They are a continuation of the intercalated duct which thus appears as if telescoped within the acinus.

2. Ducts. Two are present in the pancreas: the main duct (duct of Wirsung) and an accessory duct (duct of Santorini).

a. Intercalated (intermediate) ducts. They are the smallest, and connect directly with the acini. Lined with rather flat cells. They are intralobular.

b. Excretory ducts. Their lining is low columnar epithelium in the smaller branches, high columnar in the larger. Goblet cells occur. Outside the basement membrane there is a layer of connective tissue.

C. Endocrine portion: Islands of Langerhans. In routine slides they appear as irregularly spherical masses of pinkish cells, arranged in the form of anastomosing cords. Numerous blood capillaries occur among them. The size of the islands is variable. They are more abundant in the tail of the pancreas than in the head. With special techniques three cell types are recognizable:

1. Alpha or A cell. Granules insoluble in alcohol. These cells constitute only a small proportion of the cells of the island.

2. Beta or B cell. Form the bulk of the island. They contain alcohol soluble granules.

3. D cell. The least abundant. Filled with small granules (staining bluish with the Masson stain).

XII. The Liver

Although the liver performs multiple functions it has a single type of epithelial secretory cell, the hepatic cell. It differs from other glands in that it receives most of its blood supply through the portal

vein. The finer branches of the latter open into a system of irregular capillaries (hepatic sinusoids) which empty in the hepatic veins.

A. Stroma. The liver is incompletely invested by a serous coat (visceral peritoneum) which covers a delicate connective tissue capsule (of Glisson). At the porta hepatis the capsule surrounds the blood vessels and enters with them into the gland, forming a framework and dividing it into small lobules. Fine argyrophil meshworks penetrate the lobules.

B. Lobules. In man, the interlobular connective tissue is sparse and the separation of the lobules from each other is not as complete as in certain mammals (pig). The roughly prismatic hepatic lobule is the anatomical unit of the liver.

1. Hepatic cords. They are slightly anastomosed cords of hepatic cells, which extend radially from the central vein to the periphery of the lobule. Each cord usually consists of a double row of cells.

a. Hepatic cell. The liver cells are polygonal in shape; they usually have a single spherical nucleus, but binucleated cells are not uncommon. The cytoplasm contains fat droplets and variable amounts of glycogen.

b. Bile capillaries. A very narrow bile capillary runs between the adjacent surfaces of the hepatic cells. Each begins at the blind end (next to the central vein of the lobule), runs through the length of the cord and empties into a small bile duct at the periphery of the lobule.

2. Hepatic sinusoids. The hepatic cords are separated by irregular, anastomosing blood spaces (sinusoids) which connect the smallest branches of the portal veins with the central vein of the lobule. Two cell types occur in their walls:

a. Endothelium. Flat cells with deeply staining nucleus.

b. Stellate (Kupffer) cells. These are fixed histiocytes (p. 13) with rather large, clear nucleus; their cytoplasm often extends into processes and they seem to be anchored to the wall of the sinusoid. They are best seen in mammals after repeated injection of India ink. Transitions between the endothelium-like cell and the Kupffer cell have been described.

c. Reticulum. The wall of the sinusoid is reinforced by delicate meshworks of argyrophil fibers continuous with collagenous fibers in the wall of the central vein and interlobular connective tissue.

C. Bile ducts. The small bile ducts are lined with cuboidal epithelium; they are richly anastomosed and they give rise to increasingly larger ducts lined with columnar cells.

D. Portal canals. The interlobular bile ducts always accompany the branches of the portal vein and the hepatic artery. These three sets of structures, enclosed within connective tissue, constitute a portal canal.

E. The hepatic artery. It is relatively small and supplies the interlobular connective tissue and its contained structures. Some of the arterial capillaries empty into the smaller branches of the portal vein or anastomose with the hepatic sinusoids.

F. The hepatic veins. They course within the liver independently from the portal vein, i.e. they do not run in portal canals.

1. **Central veins.** The central veins of the lobules are the initial portions of the hepatic veins. Their walls have longitudinal collagenous fibers. Each central vein receives numerous sinusoids as it passes through the center of the long axis of the lobule which it leaves at the base. It joins central veins of other lobules to form the:
2. **Intercalated (sublobular) veins.** They can be identified in sections because they do not accompany the arteries and bile ducts.
3. **Collecting veins.** Arise through fusion of several of the preceding. The collecting veins finally merge into the hepatic veins.

G. The extrahepatic bile ducts. These are the hepatic ducts and the common bile duct. Their mucosa, thrown into folds, has a tall columnar epithelium. There is a scanty submucosa.

H. The gall bladder. Its wall is composed of three layers:

1. **Mucosa.** It is thrown into elaborate, anastomosing folds.
   a. **Epithelium.** High columnar with oval nuclei situated in the basal half of the cells.
   b. **Tunica propria.** Connective tissue with abundant capillaries.
   c. **Glands.** Small tubulo-alveolar glands occur near the neck of the bladder. Their epithelium is cuboidal, and the nuclei are pressed against the base of the cell. Probably mucus-secreting.
2. **Muscularis.** Consists of an irregular network of longitudinal, circular and oblique smooth muscle fibers.
3. **Perimuscular layer.** Composed of fibrous connective tissue. The portion of the gall bladder not attached to the liver is covered by the peritoneum, which forms a serous coat.

THE RESPIRATORY SYSTEM

Two main parts are distinguished: the conducting and the respiratory portions. The latter comprises the pulmonary alveoli. The conducting portion consists of a series of passages (nasal cavity and nasopharynx, larynx, trachea and bronchi) through which air reaches the lungs.

I. Nasal Cavity and Nasopharynx

The mucosa of the nasal cavity is not of uniform type. The same is true of the nasopharynx.

A. Nasal cavity. It extends from the nostrils to the choanae and is divided into vestibular, olfactory and respiratory regions. Its lining is continuous with the mucosa of the nasal sinuses.

1. **Vestibule.** Lined by stratified squamous epithelium continuous with the skin of the nose. The anterior part of the vestibule has numerous large hairs which aid in preventing the entrance of air-borne particulate matter.
2. **Olfactory region** (see p. 95).
3. **Respiratory region.** Lined by pseudostratified ciliated epithelium with numerous goblet cells. There is no distinct tunica propria or submucosa. Sero-mucous glands are numerous. Leucocytes, lymphocytes and plasma cells also abound.
4. **Nasal sinuses.** The mucosa of the maxillary, ethmoid, frontal and sphenoid sinuses is also lined by pseudostratified ciliated epithelium, but it is somewhat thinner and has fewer glands.

B. Nasopharynx. The epithelium of the nasal portion is pseudostratified ciliated; the oral portion is lined by stratified squamous epithelium. Mucous and mixed glands are present. Lymphoid tissue abounds in the upper part. The pharyngeal tonsil (p. 42) occurs in this region.

II. The Larynx

The walls of the larynx are supported by a series of cartilages which are articulated with each other. It also has an intrinsic musculature composed of striated muscle fibers.

A. Structure. It consists of a mucosa, submucosa, the cartilages and the intrinsic muscles.

1. **Mucosa.** Its epithelial lining is pseudostratified ciliated except

in the anterior surface and half of the posterior surface of the epiglottis, ary-epiglottic folds and vocal folds (true vocal cords) which are covered with stratified squamous epithelium. The tunica propria is rich in elastic fibers and is infiltrated with lymphocytes.

2. **Submucosa.** It is poorly defined and less dense than the tunica propria. It contains sero-mucous glands except in the vocal cords.

3. **Cartilages.** They are of the hyaline variety except the epiglottic, corniculate, cuneiform and upper part of the arytenoid which are elastic (p. 15). The thyroid and cricoid cartilages become calcified after the second decade of life.

4. **Intrinsic muscles.** They are formed by typical skeletal muscle fibers.

III. The Trachea and Main Bronchi

The trachea and main bronchi are also supported by cartilages which prevent the collapse of their walls. They are absent in the posterior wall, which contains bundles of smooth muscle fibers.

A. Structure of the wall. It consists of a mucosa, submucosa, cartilages and, in the posterior surface, a muscular coat (trachealis muscle).

1. **Mucosa.** A muscularis mucosae is absent.

   a. **Epithelium.** Pseudostratified ciliated. Numerous goblet cells are present.

   b. **Tunica propria.** Contains numerous elastic fibers, especially abundant in its deeper zone where the muscularis mucosae would be located. Lymphocytes abound in this layer.

   c. **Glands.** They are sero-mucous. They open by short ducts on the free surface of the epithelium. The larger glands are located in the submucosa; in the posterior wall they even invade the muscular layer.

2. **Submucosa.** Formed by loose connective tissue with fat cells.

3. **Cartilages.** These are of the hyaline variety. They are C-shaped, with the ends directed posteriorly. The thickness and width of each cartilage vary somewhat, and their ends may bifurcate. Each is surrounded by dense fibrous connective tissue which extends transversely from end to end; a similar fibro-elastic membrane connects the adjacent plates.

4. **Muscularis.** This is restricted to the posterior, soft wall of the

trachea. It is composed of a thick layer of smooth muscle bundles which run mainly transversely. They are inserted into the inner surface of the ends of the cartilage plates and to a lesser extent into the fibro-elastic membrane connecting the plates.

IV. The Lungs

They consist of a system of branching tubules (bronchi) which constitute the intra-pulmonary conducting portion; the smallest branches (respiratory bronchioles) open into the sac-like pulmonary alveoli where the interchange of oxygen and carbon dioxide between the air and blood takes place. The alveoli, bronchi and the vessels are bound together by connective tissue rich in elastic fibers. The lungs are covered by a serous membrane, the visceral layer of the pleura.

A. The visceral pleura. It is lined by mesothelium, and is continuous with the parietal pleura. It consists of connective tissue which contains some smooth muscle fibers and several prominent layers of elastic fibers running in different directions.

B. Stroma. From the pleura delicate septa enter the lung dividing it into a large number of lobules (secondary lobules). These are visible on the surface of the adult lung because of the dust deposits in the interlobular septa. Each secondary lobule contains many primary lobules or pulmonary units. The stroma enters the lobules and separates the alveoli; it consists then of fine argyrophil fibers and extensive elastic networks.

C. The bronchial tree. It arises within each lung through repeated branching of the main bronchus. The walls of the intrapulmonary bronchi are reinforced by cartilages. Smooth muscle is also present. The minor divisions of the bronchial tree receive special names.

1. Large and medium-sized bronchi. They differ from the trachea in that their walls are completely surrounded by cartilage plates of irregular shape.

a. Mucosa. Same as in the trachea but it has longitudinal folds. The epithelium is pseudostratified ciliated. Sero-mucous glands are normally present, decreasing in numbers as the bronchi become smaller. A tunica propria is present; it contains many elastic fibers.

b. Muscle layer. The bundles of smooth muscle fibers are ar-

ranged into a spiral meshwork around the tube. It is intimately associated with the elastic fibers (myo-elastic layer).

c. Cartilage plates. They occur in a fibro-elastic layer. The plates are irregular and decrease in size in the smaller bronchi. The portion of the fibro-elastic layer external to the plates blends with the stroma of the lung. The bodies of the sero-mucous glands occupy this layer.

d. Peribronchial lymph nodes. They occur scattered along the bronchi, especially where they branch. Coal and dust particles may be seen within the nodes.

2. Small bronchi (bronchioles). With the progressive decrease in the size of the bronchi their walls become thinner and may be reduced to a single cell layer. Cartilage disappears when the diameter of the bronchiole reaches 1 mm. The glands also disappear but goblet cells still occur.

3. Terminal bronchioles. They measure about 0.5 mm. in diameter. Their mucosa is folded longitudinally. They are lined by simple columnar or cuboidal ciliated epithelium. Goblet cells are absent. The amount of muscle is relatively increased.

4. Respiratory bronchioles. Each terminal bronchiole divides into two or more branches called respiratory bronchioles because a few alveoli open into them. They thus mark the transition between the conductive and respiratory portions, respectively. Their first portion is lined with ciliated columnar epithelium which becomes low cuboidal, non-ciliated in the second portion. Smooth muscle bundles still occur in their walls.

D. Alveolar ducts. The respiratory bronchioles branch into a variable number of long tubules (alveolar ducts) which are beset with thin-walled outpocketings, the alveolar sacs, also with single alveoli. The intervening portions consist of strands of elastic and collagenous fibers and smooth muscle cells.

E. Alveolar sacs and alveoli. The alveolar sacs contain two or more alveoli. The thin walls of the latter have numerous anastomosing capillaries which form a very close network. The alveoli connected with different alveolar ducts are interlaced so that it is not always easy to recognize the system to which they belong.

1. Lining of the alveoli. Its nature is a much debated point. Two opposite views are held:

a. The walls of the alveoli are lined by squamous epithelial

cells and broad non-nucleated plates supposedly arising from the fusion of cells which have lost their nuclei.

b. The alveolar walls consist of a thin ground membrane in which the argyrophil and elastic fibers run. The nucleated cells may be the so-called:

2. Septal cells, which are probably of histiocytic nature.

3. Dust cells (alveolar phagocytes). They occur in the alveoli and may contain particles of dust. They are identical with the histiocytes (macrophages) of other parts of the body (p. 12). They probably arise from the septal cells.

F. Blood vessels. The lungs receive arterial and venous blood.

1. Arterial blood. This is supplied by the bronchial arteries which branch in the walls of the bronchial tree and the blood vessels. It is returned to the systemic circulation through the pulmonary and bronchial veins.

2. Venous blood. Reaches the lungs through the pulmonary arteries. The latter accompany the branches of the bronchial tree to the termination of the respiratory bronchioles. As the alveolar duct is reached, the arterial branch forms the extensive capillary bed in the alveolar walls. The capillaries give rise to veins which at first course independently in the interlobular septa, joining the bronchi later to emerge from the lung as the pulmonary veins.

THE URINARY SYSTEM

The secretory portions of the system, the kidneys, are compound tubular glands which elaborate the urine. They are connected with excretory passages the walls of which have a rather uniform structure.

I. The Kidney

It consists of a cortex which covers the medullary substance, composed of 8 to 18 renal pyramids (of Malpighi); their apices (papillae) project into the lumen of each minor calyx.

A. Capsule. Connective tissue with collagenous bundles and a few elastic networks.

B. Stroma. This is much reduced in the human. It consists of thin collagenous fibers and many argyrophil fibers, with few fibroblasts. Collagenous bundles and elastic fibers occur only in the walls of the vessels.

C. Uriniferous tubules. The parenchyma of the gland consists of a very large number of uriniferous tubules. Two portions can be distinguished in each tubule: a terminal (secretory) concerned with the formation of the urine, and an excretory formed by collecting tubules which convey the urine to the pelvis and ureter. The origin of the two portions in the embryo is different (p. 141). The terminal tubule constitutes a distinct structural and physiological unit termed nephron.

1. Terminal tubule. This is very long (30-40 mm.) and tortuous. It presents a series of successive segments, each of which has a characteristic type of epithelium. It begins in a:

a. Malpighian (renal) corpuscle. This is a more or less spherical body of variable size. It consists of:

(1) Bowman's capsule. It forms the blind, expanded end of the uriniferous tubule and is lined by flattened epithelial cells.

(2) Glomerulus. This is formed by a tuft of looped capillaries which projects into Bowman's capsule and reduces its cavity to a crescentic, narrow space continuous with the lumen of the tubule. The capillaries of the glomerulus do not anastomose and are enmeshed by argyrophil fibers with a few fibroblasts.

(3) Afferent arteriole. The capillary loops of the glomerulus arise from this vessel (p. 73).

(4) Efferent arteriole. Instead of merging into a vein the glomerular capillaries form an efferent arteriole of the same or slightly smaller caliber. Thus the glomerulus is a conglomerate of tortuous capillaries interposed in the course of an arteriole.

b. Proximal convoluted tubule. Is the longest (about 15 mm.) and most convoluted portion, located in the immediate vicinity of the glomerulus. It is lined by a layer of cuboidal cells with round nuclei and acidophilic cytoplasm. Their basal portions have a distinctly striated appearance. The terminal portion of the convoluted tubule enters the medulla where it passes into:

c. Henle's loop. It has a descending and an ascending limb connected by a sharp bend. The latter is located at varying levels of the medulla. The diameter of the tubule varies:

(1) Thin segment. The terminal portion of the proximal convoluted tubule forms the upper part of the descending

limb; it changes abruptly into the thin segment which is lined by a single layer of flattened epithelial cells.

(2) Thick segment. Occurs in the ascending limb, which enters the cortex and closely approaches the glomerulus with which the tubule begins. It is lined with cuboidal cells with granular cytoplasm.

(3) Variations in length. The length of the entire loop and the extent of the thin segment varies in different tubules, according to the position of their Malpighian corpuscles, i.e. the nearer the latter are to the medulla the longer the loops and their thin segments, which extend into the ascending arm.

d. Distal convoluted tubule. It begins near the glomerulus and terminates by connecting with the arched collecting tubule. It is much less convoluted than the proximal tubule and is lined by low columnar or cuboidal cells with granular, slightly acidophilic cytoplasm. Since the cells are not as broad as in the proximal convolution their nuclei appear closer to each other, especially on the side next to the afferent arteriole (macula densa).

2. Collecting tubules. The epithelium of the collecting tubules is cuboidal or columnar with clear cytoplasm and deep-staining nuclei. The cell outlines are usually clearly seen.

a. Arched collecting tubules. These are the initial portions, located in the cortex. They empty into the:

b. Straight collecting tubules. They receive a number of the preceding as they cross the cortex on their way to the medulla. In the inner zone of the medulla they unite with other straight tubules and finally form the:

c. Papillary ducts (ducts of Bellini). These are the largest (over 200μ) and are lined with columnar epithelium. They open at the apex of the papilla (area cribrosa).

D. The renal cortex. The renal pyramids can be considered as the lobes of the kidney, separated from each other by connective tissue during fetal life. The base of each pyramid is capped by the cortex.

1. Renal columns (of Bertini). The portions of cortex which invest the lateral surfaces of adjacent pyramids merge into these cortical prolongations, visible in the gross.

2. Medullary rays (of Ferrein). They appear in each pyramid as

thin, radially arranged processes extending from the medulla into the cortex. Each is formed by several straight collecting tubules, the loops of Henle and the terminal portions of the proximal convoluted tubules.

3. **Lobules.** Each is composed of the nephrons which open into the straight collecting tubules of a medullary ray. The lobules are not separated from each other by connective tissue; between them are located the interlobular arteries (see below).

E. **The renal medulla.** The only portions of the nephrons present in the medulla are the loops of Henle. Toward the cortex the thick segments of the ascending limbs of the loops occur in large numbers intermixed with the collecting tubules. Toward the papilla collecting tubules, ducts of Bellini and the thin segments of Henle's loops predominate.

F. **Blood vessels.** They are arranged in a definite fashion.

1. **Arteries.** Practically all the arterial blood flows through the glomeruli before it is distributed to the rest of the kidney. The renal artery breaks up into a number of large branches, the:

a. **Interlobar arteries.** These pass between the papillae to the boundary zone between the cortex and medulla, where they bend sharply to form the:

b. **Arciform (arcuate) arteries.** They run parallel to the surface between the cortex and medulla. Each gives off a large number of:

c. **Interlobular arteries,** which ascend perpendicularly to the surface about midway between the lobules.

d. **Afferent glomerular arterioles.** Each interlobular artery gives off slender branches which enter the glomeruli of adjoining lobules (p. 71).

e. **Efferent glomerular arterioles.** After they leave the glomeruli they form an extensive capillary bed for the cortex. The efferents of glomeruli located near the medulla enter the latter as the:

f. **Arteriolae rectae spuriae,** which descend as straight vessels toward the apex of the papillae, giving off branches which form a capillary network.

2. **Veins.** Their arrangement is similar to that of the arteries, which they accompany throughout the organ. The veins of the cortex arise from capillaries near the surface (stellate veins). They

continue into interlobular veins, which empty into arciform veins; the latter receive the venulae rectae of the medulla. The arciform veins merge into interlobar veins.

II. The Renal Pelvis and Ureter

The excretory passages convey the urine from the kidney to the outside. The pelvis of the kidney and the ureter constitute the main excretory duct. They will be considered together.

A. **Structure of the wall.** It consists of three coats:

1. **Mucosa.** Composed of epithelium and tunica propria. It is usually thrown into longitudinal folds in the ureter. True glands do not occur.
   a. **Epithelium.** Transitional; its thickness varies, depending on the state of distension (p. 7).
   b. **Tunica propria.** Loose connective tissue with abundant cells.
2. **Muscularis.** Consists of an inner longitudinal and an outer circular layer; a third, discontinuous outer longitudinal layer occurs in the lower part of the ureter.
3. **Fibrous coat.** Loosely arranged connective tissue containing the larger portions of the vessels. It blends with the connective tissue of the surrounding structures.

III. The Urinary Bladder

Its walls are similar in structure to those of the ureter, but they are much thicker due to the greater development of the muscle. There is no distinct submucosa.

A. **Structure of the wall:**

1. **Mucosa.** It is thrown into folds when the organ contains little or no urine. It lacks glands except in the vicinity of the internal urethral orifice where a few rudimentary, mucus-secreting glands usually occur.
   a. **Epithelium.** Same as in the ureter.
   b. **Tunica propria.** Loose connective tissue; lymphocytes abound. It becomes quite thick in the contracted bladder.
2. **Muscularis.** The three smooth muscle layers of the lower part of the ureter are continued on the bladder, where their bundles interlace and anastomose. However, their identity is not completely lost and an inner and outer longitudinal layer, separated by a thick middle circular, can still be recognized.

3. **Fibrous coat.** Similar to that of the ureter. The upper part of the bladder is covered by the peritoneum.

IV. The Urethra

The structure of the urethra differs somewhat in the two sexes. It is shortest and of more uniform structure in the female.

A. Female urethra. Its wall has a mucosa, and a rather indefinite muscularis. A sphincter is also present.

1. **Mucosa.** It is thrown into longitudinal folds.

   a. **Epithelium.** It is usually stratified squamous, with areas of pseudostratified columnar (p. 7).

   b. **Urethral glands (of Littré).** Opening at the bottom of the recesses, between the folds of the mucosa, are these branched tubular glands which may extend beyond the tunica propria. The terminal portions are lined by clear, mucus-secreting columnar cells.

   c. **Tunica propria.** Loose connective tissue with abundant elastic networks. It contains a network of large irregular venous spaces (corpus spongiosum).

2. **Muscularis.** Outside the corpus spongiosum there are both longitudinal and circular smooth muscle fibers, the latter being external.

3. **Sphincter.** Consists of circularly arranged, striated muscle fibers located in the periphery.

B. Male urethra. Three parts are distinguished: a short proximal, surrounded by the prostate (p. 80), the prostatic portion; a second, also short, the membranous portion; and a third, long, the cavernous portion.

1. **Mucosa.** The type of epithelium varies.

   a. **Epithelium.** Transitional in the prostatic portion; stratified or pseudostratified columnar in the membranous and cavernous portions, replaced toward the navicular fossa by stratified squamous. Patches of the latter often occur in the cavernous portion.

   b. **Glands.** Glands of Littré occur; they are largest and most numerous in the cavernous portion.

   c. **Tunica propria.** Loose connective tissue with many elastic networks. It contains numerous scattered bundles of smooth

muscle, mainly longitudinal. Circular bundles present near the periphery.

2. Corpus spongiosum (or cavernosum). Surrounds the cavernous portion of the urethra and is more developed than in the female. It is enclosed in a fibrous connective tissue capsule (albuginea).

THE MALE GENITAL SYSTEM

The male genital system consists of the testes, a complex system of excretory ducts with their auxiliary glands (seminal vesicles, prostate and bulbo-urethral glands) and the penis.

I. The Testis

The testis is a compound tubular, cytogenic gland (i.e. produces germ cells or spermatozoa) surrounded by a white, fibrous capsule, the albuginea. The terminal portions of the seminiferous tubules are lined by the seminal epithelium.

A. Albuginea. It is densely fibrous. In the anterior and lateral surfaces of the testis it is covered by a mesothelial lining (tunica vaginalis). At the posterior surface of the organ it is thickened to form the mediastinum testis. From the latter thin discontinuous partitions, the septula testis, extend radially to the capsule and divide the organ into about 250 lobules.

B. Lobules. The lobules are conical; their apices converge toward the mediastinum. They contain the terminal portions of one to three seminiferous tubules which are extremely tortuous (convoluted seminiferous tubules). They are continued into the initial portion of the excretory ducts, called the straight tubules (tubuli recti).

C. Rete testis. The tubuli recti pass into the mediastinum where they empty into this network of thin-walled channels which communicates with the epididymis through the efferent ductules.

D. Seminiferous tubules. They do not end blindly but form arches. They may communicate with adjacent tubules by anastomoses which pass through the incomplete interlobular septa.

1. Epithelium. It rests on a basement membrane surrounded externally by a fibro-elastic layer. The epithelium may be described as stratified. It has two kinds of cells:

a. Sertoli (sustentacular) cells. They are scattered, tall cells with

ragged edges, which extend from the basement membrane to the lumen. The nucleus is pale, oval and its position varies. They act as supporting and nutritive agents for the developing spermatozoa.

b. Spermatogenic cells. They lie between the former and form several layers. The layer next to the basement membrane is formed of:

(1) Spermatogonia. Spherical or cuboidal cells with a nucleus rich in chromatin. They divide actively and produce new spermatogonia.

(2) Primary spermatocytes. They are larger cells derived from the spermatogonia. The aspect of the nucleus varies according to whether it is in the resting stage or preparing for mitotic division. Stages of the latter are often seen. They give rise to:

(3) Secondary spermatocytes. Smaller than the preceding; they are placed in a more superficial position, i.e. above the primary spermatocytes. Each divides once by mitosis, producing two:

(4) Spermatids. They line the lumen of the tubule and are the smallest of the cells of the seminal epithelium. They are transformed without further division into spermatozoa. Groups of spermatids undergoing this transformation (spermiogenesis) can be seen attached to the free surfaces of the Sertoli cells.

(5) Degenerative stages of the epithelium are frequently found even in healthy individuals. Degenerating spermatids and sometimes atypical spermatocytes occur in the lumen of the tubules. They are eventually discharged with the semen.

E. Spermatogenesis. The process of spermatogenesis consists essentially in the pairing of homologous chromosomes and their separation by a mitotic division so that the daughter cells receive one half of the number of chromosomes characteristic of the species. In man there are 48 chromosomes, including an unequal pair of sex-chromosomes (X and Y) in the male.

1. Synapsis. The pairing of the chromosomes takes place during synapsis, which occurs soon after the primary spermatocytes have been formed.

2. **Growth of the primary spermatocytes.** Synapsis is followed by a period of growth in which the double chromosomes disappear from view with the formation of a chromatin reticulum.

3. **First maturation mitosis.** The cell goes through a prophase (p. 3) in which the double chromosomes reappear. The latter are so arranged in the equatorial plate that each member of the pair is attached to a fiber of the spindle. During the anaphase the chromosomes of each pair (including the X and Y) are drawn into the opposite poles of the spindle. Since the daughter cells (secondary spermatocytes) receive one half of the total number of chromosomes this mitosis is termed reductional or heterotypic.

4. **Second maturation mitosis.** The secondary spermatocytes divide in turn. This division, however, is an ordinary (homeotypic) mitosis, i.e. each chromosome splits lengthwise. The daughter cells are now called spermatids. Four arise from each primary spermatocyte through the two successive mitoses.

5. **Spermiogenesis.** The transformation of the spermatids into spermatozoa is a complex process and will not be considered here.

F. **The spermatozoa.** Consists of a head, a middle piece and a tail.

1. **Head.** In man, the head of the spermatozoon is a flattened oval body; in profile it appears pear-shaped. It measures 4 to 5μ in length. It is the condensed nucleus of the spermatid. Enveloping the nucleus there is a thin cytoplasmic membrane, the galea capitis.

2. **Middle piece.** Is cylindrical and connects the posterior pole of the head with the tail.

3. **Tail.** Consists of a main segment 40 to 50μ in length, and a thinner terminal segment (5-10μ).

G. **The interstitial cells.** In addition to the connective tissue the stroma contains the interstitial (Leydig) cells. They are rather large, with a roundish excentrical nucleus. The cytoplasm contains numerous inclusions (lipoid granules, brownish pigment and sometimes crystaloids). They usually form small clusters. Regarded by some as the source of the internal secretion of the testis.

II. The Excretory Ducts

They begin with the tubuli recti and the rete testis, already mentioned (p. 76). The transition between the convoluted seminiferous tubules and the straight tubules is abrupt.

A. Ductuli efferentes. They are the initial portion of the extratesticular excretory ducts. Up to 14 or 16 occur in the human. Spermatozoa are seen in their lumina.

1. **Epithelium.** Consists of alternating groups of tall ciliated cells and short non-ciliated. Both types are secretory. Basal cells also occur.
2. **Tunica propria.** Connective tissue with some circular smooth muscle fibers.

B. Ductus epididymis. This is very long (4 to 6 meters) and convoluted. It contains numerous spermatozoa.

1. **Epithelium.** Is pseudostratified stereociliated (p. 7). The ciliated cells are tall columnar and reach the lumen; their nuclei are located in the basal half of the cell. They are secretory. The basal cells are round or polygonal and occur next to the basement membrane.
2. **Tunica propria.** Consists of loose connective tissue with abundant cells. Smooth muscle occurs in small quantities and is circularly arranged.

C. Ductus deferens. Is a continuation of the preceding and, as part of the spermatic cord, passes into the abdominal cavity to end in the prostatic portion of the urethra. It consists of three coats:

1. **Mucosa.** Is thrown into longitudinal folds.
   a. **Epithelium.** Of the same type as in the epididymis, but the columnar cells are lower and not always ciliated.
   b. **Tunica propria.** Connective tissue rich in elastic fibers.
2. **Muscularis.** Is the thickest coat and has three smooth muscle layers: an inner and outer longitudinal separated by a thick middle circular.
3. **Fibrous layer.** Fibro-elastic with occasional bundles of smooth muscle fibers.

III. Accessory Genital Glands

A. Seminal vesicles. They are elongated, tortuous sacs with a very irregular lumen and numerous outpocketings. Spermatozoa are infrequently seen in their lumina. Their rôle is secretory.

1. **Mucosa.** It is elaborately folded and resembles the mucosa of the gall-bladder.
   a. **Epithelium.** Varies somewhat, but it is usually pseudostrati-

fied. The columnar cells contain secretion granules and a characteristic yellowish pigment which increases with age.

b. Tunica propria. Forms a continuous layer around the vesicle. It enters the folds and contains numerous elastic fibers and some smooth muscle fibers.

2. **Muscularis.** It has two layers of smooth muscle, an inner circular and an outer longitudinal.

3. **Fibrous layer.** Composed of dense fibrous tissue with abundant elastic nets.

B. Prostate. It is a conglomerate of 30 to 50 small compound tubulo-alveolar glands with a smaller number of ducts (15 to 30) which open independently into the urethra. It produces a thin, opalescent secretion.

1. **Capsule.** Fibrous connective tissue with numerous smooth muscle fibers in its inner layer. It sends broad septa which enter the organ and form the abundant:

2. **Stroma.** It separates the secretory alveoli. It is rich in elastic fibers and contains numerous bundles of smooth muscle fibers, of variable size.

3. **Glandular epithelium.** Varies in different glands. It is usually cuboidal or columnar, and shows evidences of secretion. The ducts are lined by a columnar epithelium which becomes transitional near their opening into the urethra.

4. **Concretions (corpora amylacea).** They occur within some alveoli and increase with age. Each consists of a series of concentrical layers. If small they are evacuated with the semen.

C. The bulbo-urethral (Cowper) glands. They are compound tubulo-alveolar glands in which the tubules and ducts have a very irregular diameter. They produce a secretion resembling mucus.

1. **Glandular epithelium.** Cuboidal or columnar. Most of the columnar cells are of mucous type. Others are acidophilic and have a granular appearance.

2. **Stroma.** Fibro-elastic connective tissue with few muscle fibers. Externally the glands are enclosed by a layer of striated muscle.

IV. The Penis

The penis is formed by three cylindrical bodies of erectile tissue—the two cavernous bodies and the cavernous body of the urethra

(corpus spongiosum, p. 75) which terminates distally in the glans penis. Externally the penis is surrounded by skin.

A. Cavernous bodies.

1. **Albuginea.** Each is surrounded by a thick fibrous membrane, the tunica albuginea. It forms a fibrous partition between the two bodies which, near the end of the penis, is pierced by many clefts through which the cavernous spaces of both sides communicate.
2. **Cavernous spaces.** They are separated by trabeculae of dense fibrous connective tissue with some smooth muscle fibers. Lined by endothelium continuous with the endothelium of the arteries and veins.

B. Glans penis. Consists of dense connective tissue containing large, thick-walled anastomosing veins.

C. Blood vessels. They are very numerous and take an important part in the mechanism of erection, in which the arteries play the active, the veins the passive, rôle. The lacunae of the cavernous bodies are filled with arterial blood which accumulates under increasing pressure and the erectile tissue becomes rigid.

THE FEMALE GENITAL SYSTEM

It consists of the ovaries in which the ova (egg cells) are formed; a system of ducts—the oviducts, uterus and vagina; and the external genitalia. Functional tubular connections comparable with the efferent ductules of the testis do not occur in the ovary; the mature ova released through the rupture of the follicles are received by the open end of the oviduct and, if fertilized, they are transferred to the uterus, where embryonic development takes place.

I. The Ovary

The ovary consists of a cortical zone where the ova are located and a medullary (vascular) portion; the latter is surrounded by the cortex except at the hilus. The surface of the cortex is covered by germinal epithelium, instead of mesothelium.

A. Germinal epithelium. It produces ova in the embryo. In infants is columnar or low cuboidal, decreasing in height in the adult. A basement membrane is absent.

B. Albuginea. A dense connective tissue layer beneath the germinal epithelium.

C. Follicles. They are most numerous in young subjects; their number decreases steadily with advancing age, mostly through rupture and release of the ova (ovulation), but also due to degeneration (follicular atresia).

1. Primary follicles. They are the most numerous and occupy the periphery of the cortex. They are spherical bodies containing an ovum in the center. The ovum has a large, vesicular, usually excentric nucleus surrounded by a large amount of cytoplasm. Surrounding the ovum there is an epithelium consisting of low cuboidal (follicular) cells.

2. Growing follicles. The progressive development of the primary follicle includes growth of the ovum and the follicular cells, the formation of follicular fluid and changes in the surrounding connective tissue.

a. Ovum. Increases in size and yolk granules appear in its cytoplasm. When it reaches a diameter of 60 to 80μ a distinct membrane, the zona pellucida, appears. The latter gradually increases in thickness.

b. Follicular epithelium. Through mitotic activity the single layer of cells surrounding the ovum in the primary follicle becomes a stratified epithelium. The follicle moves to a deeper position in the cortex.

(1) Formation of follicular fluid. When the follicle is about 0.2 mm. in diameter several spaces filled with fluid (liquor folliculi) appear among the follicular cells.

(2) Displacement of the ovum. Due to the increase in amount of the follicular fluid the separate cavities merge together; the ovum with its surrounding follicular cells is pushed to one side of the follicle. The mass of cells surrounding the ovum is called cumulus oophorus, also discus proligerus.

c. Formation of the theca folliculi. The connective tissue around the growing follicle differentiates into a capsule, the theca folliculi in which two layers can be recognized.

(1) Theca interna. An extensive capillary bed develops next to the follicular epithelium, while the connective tissue cells increase in size and become loosely arranged.

(2) Theca externa. The outermost layer is more dense and consists of concentrically arranged, spindle-shaped cells and thick collagenous fibers.

3. Mature (Graafian) follicles. They are large vesicles (10-15 mm.) which not only occupy the whole thickness of the cortex but bulge in the surface of the ovary. The follicular epithelium (termed now the granulosa) is thinner and does not show signs of mitotic activity.

a. Ovum. The ovum is quite large (120µ or more) and has a thick zona pellucida. The nucleus is also enlarged and has a delicate chromatin network and a large nucleolus. Yolk granules are more abundant in the cytoplasm.

b. Corona radiata. This is formed by those follicular cells in contact with the ovum to which they remain attached. The follicular epithelium consists of several layers of cuboidal cells.

c. Theca folliculi. The theca interna is now very prominent and its numerous large epithelioid cells show fatty granules in their cytoplasm.

4. Rupture of the follicles (ovulation). Due to increasing intrafollicular pressure the part of the follicular wall bulging on the surface of the ovary becomes gradually thinner. The wall finally breaks in a small spot and the follicular fluid with the ovum is discharged. Cells of the corona radiata remain attached to the ovum. Ovulation in the human occurs during the premenstrual period (p. 86).

5. Atresia of follicles. Follicles may degenerate at any stage of their development. The details of the process vary somewhat according to whether it takes place in a primary follicle or in one undergoing development.

D. Ovogenesis. In the human the process of development of the ovum from the stage of ovogonium to the maturation mitoses is a long one. The final result is the same as in the spermatogenesis, namely, the reduction of its chromosomes to one half of the number of the species. An important difference, however, is that of the four cells resulting from the maturation divisions only one is functional; the other three (polar bodies) degenerate.

1. Ovogonia. These occur in the ovary during fetal life. They increase in numbers through mitotic division.

2. Synapsis. The pairing of the chromosomes takes place before birth.

3. Primary ovocytes. After synapsis the female germ cells are known as primary ovocytes. The paired chromosomes disappear

from view with the formation of a chromatin network. Primary ovocytes may remain in this resting stage for many years.

4. **First maturation mitosis.** As in most mammals, it probably occurs in the human shortly before rupture of the Graafian follicle. The spindle is oriented perpendicular to the surface of the ovum. One of the daughter nuclei remains in the ovum, the other, surrounded by a small mass of cytoplasm is extruded as the first polar body. The separation of the paired chromosomes probably takes place during the first maturation mitosis.

5. **Second maturation mitosis.** This produces a second polar body which also degenerates. In most mammals it occurs after the ovum has left the follicle.

E. **Formation of the corpus luteum.** The ruptured follicle does not degenerate immediately but is transformed into this glandular structure, so called because of its yellowish color. The three layers of the follicle participate in its formation.

1. **Granulosa.** After rupture the granulosa appears folded and the collapsed follicular cavity becomes filled with fluid containing some blood. The follicular cells increase in size and become spherical; yellowish lipoid granules appear in their cytoplasm (granulosa-lutein cells).

2. **Theca interna.** The large epithelioid cells form groups at the periphery of the granulosa, especially in the recesses between its folds. They also acquire yellowish pigment (theca-lutein cells). In the fully developed corpus luteum they have smaller size and more deeply staining nuclei.

3. **Theca externa.** Connective tissue from the theca externa enters the other two layers and the follicular cavity; it forms a stroma of interlacing trabeculae with numerous capillaries.

4. **Corpus luteum of menstruation.** If there is no fertilization the corpus luteum reaches its greatest development about two weeks after ovulation and then begins to degenerate. It is also known as a false corpus luteum (spurium).

5. **Corpus luteum of pregnancy.** This is the true corpus luteum (verum). It persists until the 5th or 6th month of pregnancy after which it slowly degenerates.

6. **Corpus albicans (fibrosum).** It is the final result of degeneration of the corpus luteum. The connective tissue between the

lutein cells increases in amount. Several weeks after the onset of involution all that remains is a whitish scar with folded walls which stain very lightly.

F. Interstitial cells. These are present in small numbers in the mature human ovary; they abound in certain mammals (rabbit, cat) in which they appear as clusters of epithelioid cells outside the theca externa of the follicles. They may contain fine lipoid granules. Their endocrine nature is questionable.

G. The ovary after the menopause. The human ovary after the menopause has lost most of the germinal epithelium or else its cells are flattened. Primary as well as Graafian follicles are absent. A variable number of corpora albicantia are still seen. The vessels of the medulla show thickening of their walls.

II. The Oviduct (Fallopian Tube)

The walls of the oviduct consist of three coats:

A. Mucosa. It is thick and elaborately folded in the ampulla and the infundibulum, less so in the isthmus. In the infundibulum the blood vessels are very numerous and form a sort of erectile tissue.

1. Epithelium. Simple columnar; it is highest in the ampulla. It has two types of cells:

a. Ciliated cells. They are most numerous in the ampulla. The cilia beat toward the uterus.

b. Glandular cells. Devoid of cilia; they produce a mucoid secretion.

2. Tunica propria. Loose connective tissue with numerous cells.

B. Muscularis. It consists of an inner circular and an outer longitudinal layer of smooth muscle fibers. The latter is less developed in the ampulla and infundibulum.

C. Serous coat. Connective tissue lined externally by mesothelium.

III. The Uterus

The coats of the uterine wall have received special names: the mucous membrane is called the endometrium; the muscular layers, the myometrium; and the serous coat, the perimetrium.

A. Endometrium.

1. Cyclic changes. The uterine mucosa in sexually mature women is subject to cyclic changes which are closely related to ovulation. Every 28 to 32 days menstruation occurs, during which the endo-

metrium undergoes partial destruction and a hemorrhage takes place. Accordingly, three stages are distinguished:

a. Menstrual stage. First three or four days after the onset of menstruation. After the flow a Graafian follicle enlarges rapidly.

b. Proliferative (post-menstrual stage). Associated with active proliferation of the endometrium and the production of mucoid secretion by the epithelium. It occupies the first half of the cycle. It is also called the interval.

c. Premenstrual (progravid) stage. Ovulation and formation of the corpus luteum take place during this stage; they are associated with changes in the endometrium preparatory to the nourishment of a possibly fertilized ovum (secretory phase).

2. Structure. During the transition between b and c (interval) the endometrium has the following structure:

a. Epithelium. Simple columnar with many ciliated cells in the corpus and fundus; tall columnar, mucus-secreting in the cervix.

b. Glands. They are simple tubular; their blind portions are slightly branched in the corpus and fundus, much more so in the cervix. In the latter they are lined with very tall cells which produce abundant mucus, especially during pregnancy.

c. Tunica propria. Closely resembles reticulo-endothelium. The argyrophil meshworks are condensed into a kind of basement membrane under the epithelium of the surface and glands. Attached to the argyrophil meshworks there are numerous cells, many of which are of histiocytic nature. They give rise to 'decidual cells' during pregnancy. Lymphocytes also abound.

3. Menstruation. Before menstruation, the mucosa is quite thick and the glands are tortuous due to hypertrophy of their cells, which store glycogen and fat. The cells of the reticulum become enlarged. The deepest layer of the mucosa including the blind ends of the glands ('basalis') does not change much in menstruation. The upper part is more deeply affected and is termed the 'functionalis.'

a. Extravasation of blood. Immediately before menstruation the arterioles constrict and leucocytes invade the tunica propria, which becomes edematous. Extravasation of blood occurs, some of it due probably to relaxation of the arteries, but passage of erythrocytes through the vessel walls (diapedesis) also takes place. Masses of erythrocytes occupy the mucosa.

b. Desquamation. With the onset of menstruation there is desquamation of the surface epithelium and discharge of the blood and tissue débris into the uterine cavity. The upper portions of the glands are also lost. Actual hemorrhage may take place, mostly from the veins. The mucosa of the cervix is not affected by menstruation.

c. Regeneration. After the menstrual flow has stopped, regeneration occurs rapidly. The epithelium and glands regenerate from the basal, intact portions of the glands. The regeneration is complete in a day or two.

B. Myometrium. Is the thickest of the three coats. It consists of bundles of smooth muscle fibers held together by connective tissue. The layers in which the myometrium is usually divided are not distinct in the adult, however.

1. **Stratum submucosum (subvasculare).** This is the innermost layer and is composed of fibers running longitudinally. Absent in the cervix.
2. **Stratum vasculare.** The thickest layer; it has mainly circular and spirally arranged fibers. Its name is due to the fact that it contains many blood vessels, especially veins.
3. **Stratum supravasculare.** Relatively thin. Composed of both circular and longitudinal fibers; the latter predominate.
4. **A thin subserous layer** of longitudinal fibers also occurs.

C. Perimetrium. It is the portion of the peritoneum which covers the corpus and a portion of the cervix. It is firmly attached to the underlying muscularis and consists of loose connective tissue lined externally by mesothelium.

D. Blood vessels. Branches from the uterine arteries enter the stratum vasculare of the myometrium. From here radial branches run directly to the endometrium and form:

1. **Coiled (helicine) arteries.** After loss of the functionalis at menstruation their ends may project into the uterine lumen and their peripheral portions undergo necrosis; bleeding from these arteries is prevented by arterial constriction. The basalis is supplied by arterioles from the adjacent muscle.
2. **Veins.** They form a plexus in the tunica propria; it communicates with a plexus of larger veins situated in the stratum vasculare.

IV. The Vagina

The walls have three coats:

A. Mucosa. It has transverse folds (rugae) and shows slight changes during the human uterine cycle. In animals, much more marked changes occur in connection with the ovarian cycle (oestrus); in the human they are not so uniform but they undoubtedly take place.

1. **Epithelium.** Stratified squamous. The superficial non-cornified layer is desquamated during menstruation. Glands are normally absent. The mucus lubricating the vagina originates from the uterine cervix.
2. **Tunica propria.** Loose connective tissue with abundant elastic networks and lymphoid infiltration. It forms papillae which project into the epithelium.

B. Muscularis. It has interlacing smooth muscle bundles running in two directions, with the longitudinal predominating. At the introitus there is a circular sphincter of striated muscle fibers.

C. Fibrous coat. Dense connective tissue with coarse elastic meshworks; it blends with the tissues of the surrounding structures. It contains a large venous plexus, nerves and small parasympathetic ganglia.

V. The External Genitalia

They include the clitoris, labia majora and minora, and certain glands which open into the vaginal vestibule.

A. Clitoris. Since it corresponds to the penis (p. 147) it has two small, erectile, cavernous bodies ending in a rudimentary glans. It is covered with stratified squamous epithelium continuous with the epithelium of the vestibule. Numerous sensory, highly specialized nerve endings occur in this organ.

B. Vestibular glands. Two kinds are present:

1. **Glandulae vestibulares minores.** They are located around the opening of the urethra and near the clitoris, and resemble the glands of Littré (p. 75).
2. **Glandulae vestibulares majores (glands of Bartholin).** Located in the lateral walls of the vestibule; they open on the inner surface of the labia minora. They correspond structurally to the bulbo-urethral glands of the male (p. 80).

C. Labia minora. Covered with stratified squamous epithelium; the underlying, richly vascular connective tissue contains the bodies of

large sebaceous glands. Numerous sensory nerve endings are present.

D. Labia majora. They are folds of the skin, with a large amount of adipose tissue and a thin layer of smooth muscle. Sebaceous and sweat glands are abundant.

VI. The Mammary Gland

The mammary gland in the human female undergoes structural changes correlated with the functional condition of the sexual apparatus. Because of this it will be considered here, even though it is actually a cutaneous gland.

A. Structure. It consists of 15 to 20 lobes, separated by broad connective tissue septa containing considerable fat. Thinner septa divide each lobe into lobules. The lobes have separate (lactiferous) ducts dilated into ampullae at the base of the nipple, on the surface of which they open.

1. The resting mammary gland. It consists chiefly of connective tissue and scattered groups of excretory ducts and their branches. Whether alveoli are actually present is a matter of discussion.

a. Epithelium. The smaller branches of the ducts are lined by cuboidal epithelium which becomes pseudostratified in the main lactiferous duct.

b. Myo-epithelial cells. Occur between the epithelium and the basement membrane and are spirally arranged.

c. Intralobular stroma. Loose connective tissue with delicate collagenous fibrils; rich in cells and blood vessels. Fat cells are absent.

d. Interlobular and interlobar stroma. This is rich in thick collagenous bundles and in fat cells. Few elastic fibers present.

2. The active mammary gland. The structure of the gland changes considerably during pregnancy due to the development of very numerous alveoli which are budded off from the smaller branches of the ducts.

a. Alveoli. They are spherical, oval or irregular in shape; their size also varies. Lined by a single layer of cuboidal cells the appearance of which differs according to the stage of secretory activity.

(1) Resting condition. The cytoplasm is finely granular.

(2) Secretory phase. Minute fat droplets appear in the cyto-

plasm. They merge into larger drops in the free end of the cell.

(3) Discharge of the secretion. The swollen end of the cell breaks off, leaving behind the basal cytoplasm with the nucleus (apocrine type of secretion).

(4) Regeneration. After discharge the cell regenerates its lost cytoplasm.

b. Ducts. The epithelium of the intralobular ducts does not change during secretion; the lumina of all the ducts are wider.

c. Stroma. The stroma of the lactating gland is much reduced in amount, especially between the lobules.

d. Colostrum. At the end of pregnancy and first days after childbirth the secretion of the mammary gland is poor in fat content and has peculiar corpuscles, i.e. large cells whose cytoplasm is loaded with fat droplets (colostrum corpuscles). They are probably phagocytes which have entered the alveoli.

e. Milk. It is an aqueous solution of casein, lactose and salts, in which are suspended fat droplets (milk globules); each of the latter is covered by a thin albuminous film which prevents its coalescence with others. Some cellular débris and a few transformed leucocytes also occur.

B. Involution. The mammary gland gradually undergoes regression in old age. The epithelium of the smaller ducts atrophies. The connective tissue of the stroma becomes less cellular and the collagenous fibrils decrease considerably in numbers.

THE ENDOCRINE GLANDS

They are: the hypophysis, thyroid, parathyroids, suprarenals and pineal. The thymus, regarded by some as an endocrine, has already been described (p. 42).

I. The Hypophysis Cerebri (Pituitary Gland)

It is the most complex and probably too the most important of the endocrines. It has a double origin: the pars anterior and pars intermedia arise from the oral ectoderm, the pars nervosa, from the neural tube (p. 161). The intermedia and nervosa are intimately fused and constitute the posterior lobe, incompletely separated from the anterior by the residual cleft.

A. Pars anterior (distalis). This is the largest, and is formed of anastomosing cell cords separated by sinusoidal capillaries. Three cell types, in variable proportions according to the region, occur in the cords.

1. **Chromophobic (chief) cells.** The cell boundaries are rather indistinct. Nuclei surrounded by pale cytoplasm, with few or no secretory granules. Regarded as reserve cells by most authors.
2. **Acidophilic (alpha) cells.** They stain readily with eosin in routine slides. Their cytoplasm contains very numerous spherical granules of uniform size, except after discharge of the secretion. They are normally more numerous than the:
3. **Basophilic (beta) cells.** They are difficult to identify in ordinary slides. The cytoplasmic granules are of irregular size and shape and stain with basic dyes. The number of granules varies with the phase of functional activity of the cell.
4. **Colloid.** It is frequently found in the cell cords, but in variable amounts.
5. **Stroma.** The cords are separated by reticulo-endothelium (p. 13).

B. Pars intermedia. In man is rudimentary and its boundaries are not sharp. It consists of a few rows of pale and basophilic cells which merge with the cells of the pars anterior, and extend for variable distances into the pars nervosa. Small vesicles containing colloid often occur.

C. Pars nervosa. Is composed of branched cells of glial nature. They differ from neuroglia cells, however, in that their cytoplasm contains fat droplets. Nerve fibers also occur, as well as pigment cells and hyaline bodies of unknown origin.

D. Pars tuberalis. Covers the hypophyseal stalk (infundibulum) and part of the tuber cinereum of the brain. It is composed of faintly basophilic cells, arranged sometimes into vesicles containing colloid.

E. Pharyngeal hypophysis. Occurs frequently in man. It is an elongated body placed under the mucosa of the nasopharynx, and contains the same cell types as the pars anterior.

F. Blood vessels. The hypophysis is well supplied with blood. The posterior lobe has arteries which are independent from those that supply the anterior lobe. The sinusoids of the pars anterior receive

arterial and venous blood, the latter from veins which drain the infundibulum. The pars intermedia lacks a well-developed blood supply.

II. The Thyroid

The thyroid differs from the other endocrines in that it is made up of a very large number of colloid-containing vesicles, the thyroid follicles.

A. Capsule. This is double; the external portion is continuous with the deep cervical fascia; the internal adheres to the organ. It consists of fibrous connective tissue.

B. Stroma. Septa and trabeculae arising from the capsule divide the gland parenchyma into indistinct lobes and lobules. The septa carry the larger vessels. The follicles are invested by meshworks of argyrophil fibers.

C. Parenchyma. Contains the follicles and variable amounts of interfollicular epithelium.

1. **Follicles.** Their size and shape vary considerably, and the same is true of their contents and of the epithelium which lines them.

   a. **Follicular epithelium.** Is a single layer of cells which vary from almost flat to high columnar. Their shape is correlated with the amount of colloid contained within the follicle. The nucleus is round and the cytoplasm contains faint, basophilic granulations. Vacuoles also occur.

   b. **Colloid.** Stains pink in routine slides. In the latter it usually appears separated from the follicular epithelium by irregular spaces, due to shrinkage. Peripheral vacuoles exist, however; sometimes they occur in the center of the follicle. An excess of colloid (i.e. in colloid goiter) causes flattening of the follicular epithelium.

   c. **Reabsorption of colloid.** The colloid may rapidly disappear; when this happens the cells of the follicular epithelium become taller and larger, and often increase in numbers (hyperplasia). The follicular wall may then appear folded to a variable degree.

2. **Interfollicular epithelium.** Its presence has been denied in man; however, groups of epithelial cells, regarded as undifferentiated elements, surely occur in the interfollicular spaces. In some mammals (dog, rabbit) islands of interfollicular cells arising from the follicular epithelium are normally found.

D. Blood vessels. The blood supply is very abundant. The smaller

arterial branches have localized thickenings of the intima, and often longitudinal smooth muscle fibers. Arterio-venous anastomoses also occur. The capillary bed is very well developed and forms dense baskets around groups of follicles. The veins follow the arteries.

III. The Parathyroids

Four occur in man; they are designated as parathyroids III and IV in view of their origin (p. 125).

A. Capsule and stroma. They are separated from the thyroid by a connective tissue capsule which sends delicate septa into the irregularly lobulated parenchyma. Fat cells normally occur in the septa.

B. Parenchyma. In man two cell types are recognizable:

1. **Chief cells.** They are arranged into irregularly anastomosed cords. Their nuclei are round or oval. Some cells have clear, others have very finely granular cytoplasm (dark cells) and deeply stained nuclei.
2. **Oxyphil cells.** Present only in the human adult. They are larger than the chief cells and usually occur in groups. Their nuclei are rather small and deeply staining, and the cytoplasm contains fine granules which take the eosin in routine slides.
3. **Colloid.** Occasionally found in small follicles scattered throughout the gland. Cysts may also occur.

C. Blood vessels. The blood supply is from branches of the thyroid arteries. The capillary bed, though well developed and of sinusoidal type, is not as extensive as in the thyroid.

IV. The Suprarenal Glands

Each suprarenal (adrenal) gland consists of two distinct portions arising separately in the embryo: the cortex and the medulla.

A. Cortex. Is formed of cords of cells, separated by reticulo-endothelium and large capillaries. Three zones, merging gradually with each other, are distinguished:

1. **Zona glomerulosa.** The cells, grouped into roundish masses, are columnar and have deeply staining nuclei. The cytoplasm stains bluish and contains a few lipoid droplets. New cells are produced in this zone.
2. **Zona fasciculata.** The cords are parallel and more or less perpendicular to the surface of the gland. The cells are cuboidal and may contain two nuclei; their cytoplasm is filled with vacuoles

previously occupied by lipoid droplets containing a large amount of cholesterol. The cells appear pinkish in routine slides. The outer part of the zone produces new cells.

3. Zona reticularis. The cords lack a definite orientation and are anastomosed. The cytoplasm of the cells contains pigment but lacks the abundant vacuoles seen in the preceding zone. As a whole the cells stain pink, but to a variable degree, and some of them show degenerative changes. It is supposed that cells break down and are destroyed in this layer.

B. Medulla. The cells are roundish or slightly polygonal and form anastomosing cords separated by a sinusoidal plexus of capillaries.

1. Chromaffin cells. The majority of the medullary elements contain fine granules which appear brown after treatment with potassium bichromate. The amount of granules varies, however. They are the antecedent of the secretion of the medulla (adrenalin). In ordinary slides the chromaffin cells are stained bluish.

2. Ganglia. Minute ganglia and scattered ganglion cells occur in the human suprarenal. They receive stimuli through preganglionic fibers. The distribution of their axons is not known.

C. Stroma. The gland is surrounded by a connective tissue capsule which sends irregular septa into the cortex and medulla. The stroma between the cords is scanty and formed chiefly of argyrophil fibers and histiocytes.

V. The Pineal (Epiphysis Cerebri)

The endocrine function of this body is still a subject of controversy.

A. Capsule. It is actually a continuation of the pia mater of the brain. It sends septa which divide the organ into lobules.

B. Cell types. In routine slides only nuclei surrounded by a small amount of cytoplasm are visible. With silver techniques two cell types can be recognized:

1. Parenchyma cells. They have pale nuclei and cytoplasm prolonged into long processes ending in swellings in contact with the connective tissue septa.

2. Neuroglia cells. They have smaller, more deeply stained nuclei. They belong to the fibrous astroglia type (p. 33).

C. Acervuli (brain sand, corpora arenacea). They are concretions, resembling a mulberry, which increase in numbers with age. They

arise in areas of proliferation of the neuroglia and eventually destroy most of the glandular parenchyma.

THE SENSE ORGANS

I. The Organ of Taste

It consists of the taste buds of the tongue (p. 54) and epiglottis.

A. Structure. Taste buds are barrel-shaped cell groups embedded in the stratified epithelium in which they occur. Each is connected with the surface by the gustatory canal. Two types of epithelium are present:

1. **Taste (neuroepithelial) cells.** Long spindle-shaped elements ending externally in a short filiform process (taste hair); the nuclei are elongated and stain deeply. These cells are parallel to the axis of the bud and centrally placed.
2. **Supporting cells.** Tall columnar, with larger, oval nuclei. They are also roughly parallel to the bud axis, i.e. arranged like the parts of an orange.

B. Nerves. The terminal arborizations of fibers from the glossopharyngeal and the chorda tympani occur within the buds, where they are in contact with the taste cells.

II. The Organ of Smell

It is represented by the olfactory region of the nasal cavity, which in the human is restricted to the upper nasal conchae and a portion of the upper part of the septum.

A. Olfactory mucosa.

1. **Epithelium.** This is pseudostratified, like the respiratory epithelium, but it contains three cell types:
   a. **Supporting cells.** Tall columnar, with thickened free ends which bear one or more cilia. The nuclei are oval and pale.
   b. **Olfactory cells.** They are evenly distributed among the preceding but they are less numerous. They are true, bipolar nerve cells. They have round nuclei which form a row below the nuclei of the supporting cells. The peripheral part of the cell (i.e. the single dendrite) ends in a thin filament. The central part (axon) leaves the epithelium and joins other axons in the tunica propria.

c. **Basal cells.** Occur scattered among the bases of the supporting cells.

2. **Tunica propria.** It contains the secretory portions of the glands of Bowman. The latter are branched, tubulo-alveolar glands which produce a watery secretion.

B. **The olfactory nerve.** The axons of the olfactory cells after they leave the epithelium are gathered into bundles; the largest bundles, macroscopically visible, are the fila olfactoria which cross the cribriform plate of the ethmoid. The axons synapse with neurones (mitral cells) in the olfactory bulb.

III. The Eye

The wall of the eyeball is composed of three tunics. The outermost is thick and tough for the most part (tunica fibrosa). The middle tunic (tunica vasculosa or uvea) is rich in blood vessels. The third (tunica interna) is the retina or light-sensitive part of the eye, continuous with the optic nerve.

A. **The fibrous tunic.** It is subdivided into a large, posterior, opaque portion, the sclera, and a small, anterior, transparent portion, the cornea.

1. **The sclera.** Is composed of dense fibrous connective tissue; at the posterior pole of the eye it is perforated by the bundles of fibers of the optic nerve (lamina cribrosa). The collagenous bundles run in various directions parallel to the surface.

2. **The cornea.** Has an epithelium and a stroma (substantia propria). It has numerous sensory nerve endings.

a. **Epithelium.** Stratified squamous; connective tissue papillae are absent.

b. **Bowman's membrane.** This is the thick basement membrane under the epithelium.

c. **Substantia propria.** Composed of collagenous bundles which form thin lamellae; the bundles are parallel in each lamella. The fibrocytes are very flat and thin, with branched processes which anastomose with those of the neighboring cells. Vessels are absent.

d. **Descemet's membrane.** It is a thick elastic membrane in the posterior surface of the substantia propria.

e. **Corneal endothelium.** Composed of large, squamous cells derived from mesenchyme (mesenchymal endothelium).

B. The vascular tunic (uvea). This includes the choroid, ciliary body and iris. It is deeply pigmented.

1. **Choroid.** Is a thin, soft membrane adjacent to the sclera, from which it is separated by a potential space. Four layers are distinguished:

   a. **Suprachoroid (lamina suprachoroidea).** This superficial layer is composed of fine, transparent lamellae and fibroblasts. Flat chromatophores (pigment-bearing cells) occur between the lamellae, as well as scattered smooth muscle fibers.

   b. **Vessel layer (lamina vascularis).** Composed of numerous intercrossing arteries and veins separated by connective tissue.

   c. **Capillary layer (lamina choriocapillaris).** Consists of wide capillaries; the capillary bed is flattened and is most developed in the posterior pole of the eye. It serves for the nutrition of the outer layers of the retina.

   d. **Glassy membrane (of Bruch).** It is the innermost layer of the choroid. It is a non-cellular, double membrane.

2. **The ciliary body.** This is formed by a thickening of the choroid in front of the ora serrata (p. 167). It forms a ring to which the suspensory ligament of the lens is attached and from which the iris takes origin. It is covered internally by a retinal prolongation, the pars ciliaris retinae.

   a. **Ciliary muscle.** Smooth muscle fibers already present in the suprachoroid increase in amount in the ciliary body. The muscle fibers are oriented in three directions: meridional, radial and circular. It is innervated by the parasympathetic; fibers run in the oculomotor to the ciliary ganglion from which axons reach the muscle through the short ciliary nerves.

   b. **Vessel layer.** Formed mainly by veins.

   c. **Glassy membrane.** Continuous with the glassy membrane of the choroid but consisting of three layers.

   d. **Pigment epithelium.** It is a forward continuation of the pigment layer of the retina (p. 98) and has the same structure.

   e. **Ciliary epithelium.** Is a continuation of the sensory portion of the retina. It is formed of a single layer of columnar epithelial cells, deeply pigmented toward the root of the iris. It also covers the ciliary processes.

3. **The iris.** The iris is formed by the vascular and internal tunics of the eye. Its peripheral border (iris root) is attached to the

ciliary body; its pupillary border rests on the lens. Five layers can be distinguished: the first three belong to the vascular tunic.

a. Endothelium. Flattened mesenchyme cells, rather indistinct.

b. Anterior border layer. Connective tissue with numerous, large chromatophores. The color of the iris depends upon the thickness of this layer and its degree of pigmentation.

c. Vascular layer. Occupied by numerous vessels embedded in a connective tissue stroma. Chromatophores also occur. The sphincter of the pupil is placed in this layer; it encircles the pupil and decreases its diameter. Its smooth muscle fibers are of epithelial origin, i.e. derived from the cells of the pigment layer. It is supplied by the parasympathetic.

d. Dilatator of the pupil. Also of epithelial origin but the separation of the contractile and the pigmented epithelial portion of each cell is not complete (myo-epithelial cells). The contractile processes are arranged radially; their rôle is to increase the diameter of the pupil. Innervated by the sympathetic.

e. Pigment epithelium. As the preceding, it belongs to the pars iridica of the retina. It is so heavily pigmented that neither cell outlines nor nuclei can be seen without bleaching.

C. The retina (tunica interna). It is the most complex structure of the eye and consists of nerve cells and neuroglia. The ciliary and irideal portions have been mentioned; only the visual part will be considered here. Except at the optic papilla (disk), the fovea centralis, and the extreme periphery, ten layers are distinguished, of which 3 and 10 are the external and internal limiting membranes, covering the corresponding surfaces.

1. Pigment epithelium. The outermost layer made up of cuboidal cells with heavily pigmented cytoplasmic processes on their inner surface. Externally it is in contact with the glassy membrane of the choroid.

2. Rod and cone layer. Formed by the prolongations of the rod and cone visual cells (bipolar cells, the bodies of which occur in layer 4). The prolongations project beyond the external limiting membrane.

a. Rods. They are slender cylinders; the outer segment (containing rhodopsin) is highly refractive and longitudinally striated, while the inner is slightly thicker and finely granular. The

latter is continued into the rod fiber which crosses the external limiting membrane and connects with the cell body.

b. Cones. They are bottle-shaped and also have an outer and inner segment; the outer is short and conical, the inner expanded. The cell body is immediately beneath the inner segment. Their form is more variable than that of the rods.

3. External limiting membrane. Formed by the outer ends of Müller's fibers, the chief supporting elements of the retina (see 10).

4. Outer nuclear (granular) layer. It consists of the nuclei of the cone and rod cells. The nuclei of the latter are small and round and more deeply placed than the cone nuclei.

5. Outer plexiform layer. It lacks nuclei and represents the first synaptic layer of the retina, since it is formed by the inner prolongations (axons) of the rod and cone cells and the dendritic arborizations of the bipolar cells of the following layer. The fibers of several rods synapse with the dendritic end of one bipolar cell, but each cone synapses with a single bipolar cell.

6. Inner nuclear (granular) layer. It is thinner than the corresponding outer layer and contains the cell bodies and nuclei of the bipolar cells, also the nuclei of the amacrine and horizontal cells (association neurones) and of the fibers of Müller.

7. Inner plexiform layer. In this non-nucleated layer, synaptic association of the axons of the bipolar cells and the dendrites of the ganglion cells of layer 8 is established. The processes of the amacrine cells also occur here.

8. Ganglion cell layer. Composed of a single row of multipolar neurones. Their nuclei are large, and their numerous dendrites extend into the preceding layer. Neuroglia nuclei also occur, as well as the branches of the retinal vessels.

9. Nerve fiber layer. Consists of the axons of the ganglion cells, arranged into bundles which course parallel to the retinal surface. They converge toward the papilla, where they pass into the optic nerve. The axons are unmyelinated. Glia cells occur among them.

10. Internal limiting membrane. This is formed by the expanded, branched bases of Müller's fibers. The latter are elongated, irregular elements which extend through all layers of the retina. Their nuclei occur mostly in layer 6.

D. The optic nerve. The axons of the retinal ganglion cells pass

through the lamina cribrosa of the sclera (p. 96) as the optic nerve, where the axons become myelinated.

1. Nerve sheaths. Since the optic nerve is actually a part of the brain (p. 166) it is surrounded by prolongations of the meninges, continuous with the sclera at the eyeball.

a. Dura. This is the outermost, tough, fibrous sheath.

b. Arachnoid. A thin sheath connected with the following by delicate strands.

c. Pia. Vascular, made up of connective tissue. It sends septa into the nerve which is thus divided into bundles.

2. Neuroglia. The three types of neuroglia occur in the nerve. The nuclei of the oligodendroglia form rows between the fibers.

3. Central artery and vein of the retina. They occur in the anterior part of the nerve, close to the eye. They cross the papilla and spread on the inner retinal surface.

E. The refractive media. Besides the cornea and the fluid of the anterior and posterior chambers of the eye, they are the lens and the vitreous body.

1. The lens. Is a transparent biconvex body placed immediately behind the iris. It lacks blood vessels and nerves.

a. Capsule. A structureless elastic membrane which envelops the lens.

b. Anterior epithelium. A single layer of cuboidal cells in the anterior surface of the lens. At the equator the cells are more elongated and are arranged meridionally in rows.

c. Lens substance. Formed of long prisms (lens fibers) united by a small amount of cement. The fibers are arranged meridionally in layers, the whole lens being thus made up of concentrically disposed lamellae. The lens is held in place by the:

d. Zonula ciliaris (suspensory ligament), consisting of a system of delicate homogeneous fibers inserted in the equator of the lens and ending on the inner surface of the ciliary body.

2. The vitreous body. Occupies the space between the lens and the retina. It is a transparent, jelly-like substance formed of concentrical lamellae. In the antero-posterior axis is the hyaloid canal, occupied by a vessel in the embryo (p. 167).

F. The eyelids. They are folds of the skin, but in the posterior surface the skin is modified to form the conjunctiva palpebralis.

1. Skin. It is very thin and does not differ from the ordinary skin.

2. **Orbicular muscle.** Occurs under the skin; it consists of circularly arranged bundles of skeletal fibers.

3. **The tarsus (tarsal plate).** Dense fibrous connective tissue which extends to the lid margin. It contains the:

4. **Tarsal (Meibomian) glands.** Sebaceous glands provided with a long, straight duct beset with alveoli.

5. **Eye-lashes.** Their follicles extend obliquely up to the tarsal plate; they lack arrectores pili. Sebaceous glands (of Zeiss) and sweat glands (of Moll) occur between the follicles.

6. **Conjunctiva palpebralis.** Consists of:

a. **Epithelium.** Varies somewhat in structure; over the tarsal plates it is reduced to two layers of cells, of which the surface cells are columnar. Goblet cells occur.

b. **Tunica propria.** Connective tissue infiltrated with lymphocytes. Glands (of Wolfring) occur in it.

G. **The lacrimal gland.** Is a compound tubulo-alveolar gland closely resembling the parotid. The secretory cells are more columnar, however. The smallest ducts have a single layer of epithelial cells, which becomes a double layer in the larger ducts.

IV. The Ear

The organ of hearing consists of the external, middle, and internal ear. Only the latter will be considered here. The soft portion is the membranous labyrinth, a series of thin-walled sacs and canals connected with each other. It only partially fills the space within the osseous labyrinth, although in certain places it is in contact with its periosteum. The space between the membranous and the inner surface of the osseous labyrinth is occupied by the perilymph.

A. **General structure of the wall.** It is composed of fibrous connective tissue lined internally by a layer of flat epithelium of ectodermic origin (p. 168).

B. **Sensory areas.** In six definite areas the wall of the labyrinth is considerably modified by the presence of neuroepithelium; there is one in each of the two maculae, one in each ampulla of the three semicircular canals, and one in the cochlea.

1. **The maculae.** The macula utriculi and the macula sacculi are thickenings of the wall covered with columnar epithelium with two kinds of cells:

a. **Sustentacular cells.** Tall columnar elements with enlarged

bases which contain the nuclei; the free surface of each has a cuticular plate.

b. Hair cells. They are flask-shaped elements with their broader portion near the periphery, the narrow portion resting on the basement membrane. The expanded portions fit into the spaces between the tapering outer ends of the sustentacular cells. Each has a bundle of fine non-motile cilia—the "hair"—which projects beyond the epithelial surface and enters the:

c. Otolithic membrane, formed of a gelatinous substance containing a great number of:

d. Otoconia (otoliths), minute calcium carbonate crystals.

e. Nerve fibers. They belong to the vestibular division of the auditory nerve and terminate in contact with the hair cells. The maculae are concerned with static equilibrium.

2. The semicircular canals. Their wall does not differ from the wall of the other regions of the membranous labyrinth except at the cristae ampullares, formed of neuroepithelium.

a. Cristae ampullares. The epithelium has two kinds of cells:

(1) Sustentacular cells. Similar to those in the maculae.

(2) Hair cells. The hairs are long and enter a tall, gelatinous, longitudinally striated structure, the cupula.

b. Nerve fibers. The fibers ending in contact with the hair cells belong to the vestibular division of the auditory nerve. The cristae ampullares are concerned with dynamic equilibrium.

3. The cochlea. In man the osseous cochlea is wound 2½ times around a conical axis of spongy bone, the modiolus. The blind end of the cochlea is termed the cupula. The membranous cochlea (cochlear duct) is in close contact with the bony cochlea along the wall of the modiolus and in the opposite (external) side.

a. Osseous spiral lamina. This is a bony shelf which partly projects into the inner wall of the osseous cochlea, the turns of which it follows.

b. Spiral ligament. Opposite to the former, along the outer wall of the bony cochlea, is this projection of thickened periosteum.

c. Membranous spiral lamina. It is a connective tissue membrane stretched across the space between the spiral lamina and ligament. It divides the bony cochlea into two parallel parts containing perilymph:

(1) The scala vestibuli, arising in the vestibule in close rela-

tion to the oval window (fenestra vestibuli). It follows the turns of the bony labyrinth to the cupula, where it communicates through a small canal (helicotrema) with:

(2) The scala tympani, parallel to the former; it ends at the round window (fenestra cochleae), closed by a thin fibrous membrane.

d. Vestibular membrane (of Reissner). Arises from the periosteum covering the upper surface of the osseous spiral lamina, and extends obliquely to the upper part of the spiral ligament. It thus forms a third spiral conduit of triangular outline in cross section, the:

e. Cochlear duct (scala media). The upper wall is formed by the vestibular (Reissner) membrane, the outer by the spiral ligament, while the floor rests on the membranous spiral lamina. The inner epithelial lining is composed of flat or low cuboidal cells except those at the floor, which is occupied by the:

f. Organ of Corti. This is the sensory part of the organ of hearing. It contains sustentacular cells and neuroepithelium (hair cells). The chief elements are:

(1) Border cells. They are columnar and form a single layer in the inner end of the organ of Corti (i.e. toward the modiolus); they also line the internal spiral sulcus.

(2) Inner hair cells. They form a single row occupying only the upper part of the epithelial layer. The surface of each cell has a cuticular plate and stiff short hairs.

(3) Inner phalangeal cells. They also occur in a row along the inner surface of the inner pillar cells. The lower portion of the cell, containing the nucleus, is continued into a slender process which ends on the epithelial surface as a small cuticular plate resembling a phalanx of a finger.

(4) The inner tunnel. This is the central structure of the organ of Corti; it is a canal with triangular shape in cross section. The base of the triangle is formed by the basilar lamina, the sides by the pillar cells.

(5) Inner and outer pillar cells. They are peculiarly shaped cells, with a broad curved base containing the nucleus, and an elongated portion or pillar which consists of rigid tonofibrils (p. 3). The thickened, free end of the pillar is called the head. The head of the outer pillar has a convexity which

fits into a corresponding concavity in the head of the inner pillar.

(6) Outer phalangeal (Deiters) cells. They support the outer hair cells. They have a broad base and a slender process which passes to the surface through the space between adjacent hair cells. Each contains a bundle of tonofibrils which continues to the surface, between the hair cells.

(7) Outer hair cells. They are columnar, and have a cuticular plate on their free surface, and a number of short hairs. Their bases fit into facets in the phalangeal cells. The number of rows of outer hair cells varies.

(8) Cells of Hensen. Tall columnar; they are the outer border cells of the organ of Corti, and occur external to the outer phalangeal cells. The space between the latter and the cells of Hensen is the outer tunnel. Externally are the cells of Claudius, which are cuboidal and line the lower surface of the outer spiral sulcus.

g. The tectorial (Corti's) membrane. This is a continuation of the cuticle of the columnar epithelial cells of the limbus spiralis, and appears as a striated structure which extends outward beyond the internal spiral sulcus as far as the cells of Hensen. It is thin at the base and along the free edge.

h. Nerve endings. The branches of the cochlear division of the auditory nerve enter the modiolus and join the spiral ganglion, which is formed of bipolar cells. Their peripheral, myelinated processes reach the organ of Corti, where they terminate around the bases of the hair cells. The fibers supplying the outer hair cells cross the inner tunnel: they are often seen in routine slides.

EMBRYOLOGY

Embryology deals with the development of the individual from the moment of fertilization of the ovum to the attainment of the adult form. Used in this broad sense it comprises some of the events of early postnatal life. In the present outline only the development of the human will be considered.

PART ONE: GENERAL DEVELOPMENT

For the formation and structure of the germ cells see pp. 77, 83.

FERTILIZATION, CLEAVAGE AND THE ORIGIN OF THE GERM LAYERS

The processes of fertilization and cleavage of the human ovum have never been observed; in fact the earliest human embryos known are nearly two weeks old and have the three germ layers already formed. What follows is based on observations in mammals.

I. Fertilization

It consists essentially in the fusion of the gametes (spermatozoon and ovum), each of which carries one half the number of chromosomes characteristic of the species; the original number is thus restored.

A. Site of fertilization. In man it occurs in the upper third of the oviduct. As proof of this can be cited the fact that the embryo may be implanted in the oviduct (tubal pregnancy).

B. The process of fertilization.

1. Penetration of the spermatozoon. It usually takes place after the second maturation mitosis has been completed. The spermatozoon crosses the zona pellucida of the ovum (p. 82) and enters the cytoplasm, where it loses its tail. Its middle piece furnishes the centrosomes and spindle for the dividing ovum.

2. Formation of the pronuclei. After the second maturation mitosis the nucleus of the ovum is termed the female pronucleus.

The compact nucleus (head) of the spermatozoon becomes vesicular and shows a distinct chromatin network (male pronucleus).

3. Fusion of the pronuclei. The male pronucleus moves toward the female pronucleus; when the two finally come into contact they merge into a single (segmentation) nucleus.

4. First cleavage mitosis. Immediately after fusion of the pronuclei the segmentation nucleus enters the prophase of the first cleavage mitosis. The centrosomes contributed by the spermatozoon form a spindle.

II. Cleavage (Segmentation) of the Mammalian Ovum

Cleavage is greatly influenced by the amount of yolk present in the ovum. If the yolk is very abundant it does not affect the whole ovum (meroblastic cleavage of fishes, reptiles and birds). If it is scarce or present in moderate amounts the whole ovum will divide (holoblastic cleavage of the amphibia and mammals). Although the microscopic mammalian ovum contains little yolk its cleavage does not correspond to the segmentation of similar ova in other forms (i.e. Amphioxus) because it does not give rise to a typical blastula.

A. Early cleavage. The fertilized egg divides into two blastomeres; each of the latter divides in turn and a total of four is produced. The first two divisions are meridional. The third is equatorial and gives rise to eight blastomeres which upon further division become sixteen, etc.

B. Morula. When this stage is reached the cell aggregation shows two types of blastomeres: one light, the other dark (i.e. more granular). The light blastomeres arrange themselves as a capsule around the dark cells; the latter are termed the inner cell mass while the layer of light blastomeres is known as the trophoblast (or trophectoderm).

C. Formation of the blastocyst. Fluid collects between the inner cell mass and the trophoblast; as a result of this the morula is changed into a hollow vesicle in which the inner cell mass remains in contact with the trophoblast at one of the poles.

D. Significance of the inner cell mass. It corresponds to the blastoderm of the chick since it will give rise to the embryo, while the trophoblast becomes associated intimately with the uterine mucosa and is concerned with the nutrition, respiration and excretion of the embryo.

III. Gastrulation

Gastrulation in mammals is much more similar to the corresponding process of reptiles and birds than to the typical gastrulation observed in Amphioxus and the amphibians.

A. Formation of the endoderm. It does not arise by invagination but it is constituted by the arrangement of cells in a layer on the under surface of the inner cell mass, which is now the ectoderm.

B. Extension of the endoderm. In most mammals the endoderm spreads rapidly on the inner surface of the blastocyst, which it lines completely.

IV. Formation of the Mesoderm

The formation of the mammalian mesoderm closely resembles the production of the same layer in birds.

A. Primitive streak. It appears in the pear-shaped blastoderm and marks the axis of the embryo. It ends anteriorly in a primitive knot (of Hensen). In vertical section is seen to be a thickened band continuous with the ectoderm; its under-surface produces mesodermic cells which spread laterally and caudally between the ectoderm and endoderm.

B. Formation of the head process. This arises as a forward extension of Hensen's knot and in man and many mammals it has a cavity (notochordal canal) which opens at the primitive pit. Its floor fuses with the endoderm, after which both disappear in the area of fusion. The roof (notochordal plate) becomes the notochord.

C. Formation of the coelom. The mammalian mesoderm grows rapidly between the ecto- and endoderm. At first it is a single sheet but it soon splits into two layers, one associated with the ectoderm (somatic mesoderm) and the other with the endoderm (splanchnic mesoderm). The cavity between the two mesodermic layers is the coelom or body cavity.

D. Extra-embryonic coelom. Since the mesoderm spreads between the ecto- and endoderm throughout the blastodermic vesicle its splitting will extend beyond the embryonic area. An extra-embryonic coelom is thus formed.

EARLY DIFFERENTIATIONS OF THE GERM LAYERS; DEVELOPMENT OF THE EXTERNAL FORM

After gastrulation and the formation of the mesoderm the three germ layers of the embryo begin to differentiate and produce the primordia of the most important organic systems.

I. Early Differentiations of the Germ Layers

A. Formation of the neural tube. The neural tube is the primordium of the central nervous system; its anterior (or cephalic) portion gives rise to the brain, the rest to the spinal cord. The first indication of the formation of the neural tube is the differentiation of the:

1. **Neural (medullary) plate.** This is a thickening of the ectoderm along the longer axis of the blastoderm. It begins in Hensen's node and extends anteriorly (i.e. cephalad).
2. **Neural (medullary) folds.** The edges of the medullary plate are converted into folds, which diverge posteriorly enclosing Hensen's node. The neural plate is thus changed into a groove.
3. **Closure of the neural groove.** The neural folds increase in height and curve toward each other, finally meeting in the midline at a point which corresponds to the neck region of the adult. This changes the neural groove into a tube, the lumen of which persists throughout adult life (p. 158).
4. **The neural crest.** A longitudinal band of cells between the ectoderm and the edge of the plate sinks into the neural fold and becomes this structure.
5. **Anterior and posterior neuropores.** The closure of the neural groove does not take place simultaneously along its entire length but proceeds slowly cephalad and caudad. For a considerable period there are two openings in the ends of the tube, the anterior and posterior neuropores, respectively.
6. **Primary brain vesicles.** The anterior, expanded region of the neural tube is divided through constrictions into the three primary brain vesicles: the fore-, mid-, and hindbrain.

B. Formation of the notochord. The roof of the head process (p. 107) is known as the notochordal plate. It loses all connection with both endoderm and mesoderm and becomes a rod, the notochord, which extends beneath the neural tube and ends anteriorly under

the midbrain. The notochord is the axis around which the vertebral column will develop. Remnants are occasionally found as the pulpy nuclei of the intervertebral disks.

C. Differentiation of the mesoderm. The splitting of the mesoderm into somatic and splanchnic layers has been mentioned (p. 107). The two layers of each side are continuous near the midline, i.e. lateral to the notochordal plate.

1. Formation of the somites. At the junction of somatic and splanchnic layers the mesoderm is much thicker. This dorsal or median mesoderm becomes divided transversely into a number of more or less cuboidal, usually solid masses, the somites.

a. Order of appearance. The first somite appears behind the future occipital region of the adult. The segmentation of the dorsal mesoderm proceeds caudad until 38 pairs have developed in the neck and trunk regions of the body, in addition to those that are developed in the occipital region of the head (probably four).

b. Differentiation. Each somite becomes differentiated into three distinct portions:

(1) Sclerotome. The cells of that portion of the somite next to the notochord grow inward toward the midline to surround the notochord and lateral walls of the neural tube. They will form the body of the vertebrae and the vertebral arches.

(2) Myotome. The middle portion of the somite will give rise to a part of the skeletal (voluntary) musculature of the body.

(3) Dermatome. The outer or lateral portion of the somite is believed to be transformed into the derma of the skin (p. 46). Its existence in mammals and man has been denied, however.

2. The ventral (lateral) mesoderm. It never becomes segmented in the neck and trunk regions. The coelom occurs between its somatic and splanchnic layers.

a. Somatic layer. It is continuous laterally with the mesodermic layer which lines the outer surface of the amnion (p. 115). Mesially it passes into the:

b. Splanchnic layer, which is applied closely to the endoderm of the:

(1) Digestive tract, derived from the dorsal portion of the yolk sac (p. 114). The splanchnic mesoderm becomes converted into mesenchyme out of which the muscular coats will develop.

(2) Yolk sac. The splanchnic layer surrounding the yolk sac is the source of the first blood vessels and blood of the embryo and corresponds to the vascular area of the chick blastoderm.

3. **The intermediate cell mass (nephrotome).** This is a narrow area underlying the original longitudinal groove which separates the somite area from the ventral mesoderm. It produces the pronephroi, Wolffian bodies (mesonephroi) and the mesonephric ducts (p. 141).

II. Development of the External Form

The early appearance of the embryo differs greatly from that of the child and has features in common with the other vertebrates: this is the embryonic period, which lasts two months. After this the resemblance with the child is more striking (fetal period).

A. Embryonic period.

1. **Separation of the embryo from the yolk sac.** At the end of the formation of the mesoderm the embryonic disk (blastoderm) forms the roof of the yolk sac, the whole being connected with the chorion by the body stalk, occupied by the rudimentary allantois.

a. **Folding of the blastoderm.** A groove which appears at the periphery of the blastoderm, between the latter and the sac, marks the beginning of the separation of these two portions. As it deepens the flat blastoderm is gradually transformed into a cylinder.

b. **Formation of the digestive tract.** The endoderm of the roof of the yolk sac is incorporated into the embryo and constitutes the primordium of the digestive tract.

c. **Formation of the yolk stalk.** With the deepening of the groove the connection between the yolk sac and the embryo is very much reduced and becomes the yolk stalk.

2. **Formation of the cephalic and caudal folds.** These are due to rapid elongation of the body of the embryo.

a. **The cephalic fold.** With the closure of the neural groove the

anterior end of the embryo rises and projects beyond the yolk sac. The primitive brain vesicles become distinct.

b. The fore-gut. As the cephalic fold rises it carries along the endoderm, which forms a blind diverticulum, the fore-gut. Beneath the fore-gut the heart is developing.

c. The caudal fold and hind-gut. A less developed fold is formed at the posterior end of the embryo; it also contains an endodermic diverticulum, the hind-gut.

3. Establishment of the primary flexures. Continued elongation of the embryo during the 5th week causes the bending of the body in three different regions:

a. Cephalic flexure. This is a sharp bend at the level of the mid-brain.

b. Cervical flexure. A second more prominent flexure occuring more posteriorly, in the region of the future neck.

c. Caudal (sacral) flexure. Is present toward the posterior end of the body, which ends in a short, pointed tail.

4. Appearance of the limb buds. These are already present at the end of the fifth week. The bud for the arm is seen on each side of the body a little posterior to the cervical flexure. The lower limb buds, located in the region of the caudal flexure, are slightly smaller.

5. The branchial arches. In common with other vertebrates the human embryo shows on each side of the region of the future pharynx four grooves which separate five branchial arches. Their formation will be considered later (p. 123).

a. Mandibular arch. The first arch consists of a main portion which gives rise to the jaw, and a maxillary process appearing as a wedge between the eye and the mandibular process. Retardation of the development of the mandibular process causes an abnormally small jaw (micrognathus); its complete absence is also possible (agnathus).

b. Hyoid arch. It is separated from the mandibular by the first branchial groove which sometimes is actually a cleft.

c. Other arches. They are less developed, especially the fifth, placed behind the fourth groove and poorly defined posteriorly.

d. Cervical sinus. After the sixth week the first two arches overlap the other three, which sink into a triangular depression called the cervical sinus. Later the posterior edge of the hyoid

arch fuses with the thoracic wall and the sinus is cut off from the outside.

6. Development of the neck. The neck develops in the area occupied by the branchial arches whose mesoderm gives rise to muscles, bones and blood vessels. From the lining of the endodermic pouches several important organs arise (p. 124). When this differentiation has been completed the embryo has acquired a neck, not present in earlier stages in which the mandibular arch rests on the thorax. The neck results from an elongation of the region between the mandibular arch and the pericardium. Incomplete closure of the branchial clefts causes cervical fistulae.

7. The face. The formation of the face is a complex process. It takes place chiefly between the 5th and 8th weeks.

a. The olfactory pits. They are first represented by ectodermic thickenings (olfactory placodes) on the ventrolateral aspect of the head. The placodes sink and become converted into shallow pits.

b. Fronto-nasal process. This is the region of the head between the olfactory pits in early embryos. In later stages the olfactory pits subdivide the fronto-nasal process into:

(1) Lateral nasal processes, which with the

(2) Median nasal processes, bound the nostrils externally.

c. Fusion of the median nasal processes with the maxillary processes. This fusion forms the upper jaw. When incomplete it causes hare-lip.

d. Fusion of the lateral nasal processes with the maxillary processes. It obliterates the naso-lacrimal groove, which extends between the maxillary process and the lateral nasal process and is thus changed into the naso-lacrimal canal of the adult. This fusion also forms the wings (alae) of the nose and the cheek region. Its failure causes oblique facial cleft.

e. The nose. When first formed the nose is broad and flat with the nostrils set far apart. In later fetal months the bridge of the nose rises and the nostrils are approximated.

f. The mouth. The mouth is also very wide in early stages but during later development it is much reduced in width.

8. The external ear. This is formed around the first branchial groove (between the mandibular and hyoid arches) by the fusion

of several small tubercles in the two arches. The groove becomes the external auditory meatus.

9. The eye. During the embryonic period the eye lacks eyelids. The iris and pupil are clearly seen. The eyelids develop during the second month.

10. The limbs. At the earliest stage of their development (5th week) the limbs are lateral swellings (limb buds), the location of which has already been given (p. 111). The upper limb buds arise first.

a. Division into proximal and distal regions. The distal end of the limb bud flattens and a constriction separates this portion from a more proximal, cylindrical segment. The flattened portion becomes the hand and the foot, respectively. Radial ridges indicate the formation of the digits.

b. Subdivision of the proximal region. A second constriction separates the proximal region into two segments: the arm and forearm, and the thigh and leg, respectively.

c. Rotation of the limbs. During their development the limbs undergo changes in position. At the beginning they point caudad, but soon project outwards at right angles to the body wall. Later the palmar and plantar surfaces face the body. Further rotation brings them into the position of the adult.

d. Anomalies. They are frequent and range from complete or almost complete absence of the limbs (amelus) to a partial duplication of the hand or foot (dichirus).

(1) The distal portion may resemble a stump (hemimelus) or the proximal segments may be missing so that the hand or foot spring directly from the body (phocomelus).

(2) The digits may be fused (syndactyly), or be excessively short (brachydactyly) or they may have more phalanges than usual (hyperphalangism).

(3) More than the normal number of digits may also occur (polydactyly).

(4) Clubhand and clubfoot also result from primary defects in the development of the limb buds.

B. Fetal period. The fetus definitely resembles the child, but at the beginning of the period (3rd lunar month) the head is still disproportionately large; the embryonic flexures have disappeared. The sex can be distinguished readily.

1. Appearance of lanugo. This fine, silky hair covers the face and body during the 5th month, and begins to be shed before birth (10th lunar month) except on the face.
2. Growth of eyebrows and lashes. The eyelids fuse during the 3rd month and remain so until the 7th month. During the 6th month the eyebrows and lashes grow.
3. Growth of the nails. They begin to form during the 3rd month and project at the finger tips during the 9th.
4. Descent of the testes into the scrotum. This takes place during the 8th month.

HUMAN FETAL MEMBRANES, PLACENTATION AND DECIDUAE

I. Fetal Appendages and Membranes

The human fetal appendages and membranes are: the yolk sac, chorion, amnion, allantois and umbilical cord. They all appear early since they are concerned with important protective and nutritional functions.

A. The yolk sac. Although it does not contain yolk it is an important structure whose roof will provide the endodermic epithelium of the whole digestive system (p. 121).

1. Vitelline (omphalomesenteric) vessels. The splanchnic mesoderm which invests the outer surface of the sac is a source of blood for the embryo since the vitelline vessels arise in it.

2. Yolk stalk. This is a constriction between the sac proper and the body of the embryo. It becomes thinner as development proceeds and is located within the umbilical cord.

3. Fate of the sac. It shrinks somewhat and becomes a small, solid structure containing detritus, usually seen near the umbilical cord in the after-birth.

4. Meckel's diverticulum. This is the persisting proximal end of the yolk stalk. When it opens at the umbilicus (navel) is called an umbilical fistula.

B. The chorion. It is the continuation of the trophoblast of the blastocyst to which is added an inner lining of extra-embryonic (somatic) mesoderm. The human chorion is studded with villi, each of which contains a mesodermic core. Blood vessels enter the latter,

especially in those villi next to the uterine wall, which are incorporated into the placenta (p. 117).

C. The amnion. While in most mammals this membrane arises by a process of folding, in man and certain mammals (bat, guinea pig, apes) the amnion is formed by a different method at a very early stage of development.

1. **Origin.** A cavity appears in the solid ectodermal cell mass which remains after formation of the endoderm (p. 106). The roof and sides of the cavity become the amnion through a process of thinning, while the floor remains as the dorsal ectoderm of the embryo.
2. **Structure.** It is a thin, transparent, non-vascular membrane covered externally by mesenchyme; its interior is lined by a low cuboidal, ectodermic epithelium. It contains the amniotic fluid in which is suspended the embryo; the amount of fluid at birth is about one liter.
3. **Fate of the amnion.** After the 2nd month of pregnancy the amnion is loosely fused with the chorionic wall, with the resulting obliteration of the extra-embryonic coelom. It breaks during the early stages of childbirth and the fluid escapes as the "waters." It is expelled attached to the after-birth (p. 120).

D. The allantois. It is rudimentary in man, whereas in other mammals (i.e. the pig) it attains great development. In man, however, it is important in that it conveys the umbilical vessels to the chorion.

1. **Origin.** It appears very early, even before the gut begins to assume a tubular form. Due to this it cannot be properly regarded as an evagination of the hind-gut, as in other mammals. It occupies the body stalk, a mesodermic bridge connecting the embryo to the chorion, which it reaches.
2. **Fate.** Growth of the allantois soon ceases, and it becomes obliterated. Remnants are still discernible in the proximal part of the umbilical cord in early pregnancy.

E. The umbilical cord. The human cord is fully formed during the 6th week of pregnancy through the wrapping of the amnion around the body stalk, yolk stalk and sac.

1. **Contents.** The young cord contains the body stalk (with the enclosed allantois) and a prolongation of the coelom occupied by an intestinal loop to which is attached the yolk sac. The yolk stalk

carries the vitelline vessels. In addition there are the umbilical vessels (two arteries and a vein).

2. **Structure at term.** The walls of the cord develop a peculiar form of connective tissue ('mucous,' or jelly of Wharton) which causes the obliteration of the coelomic prolongation within the cord after the intestinal loop has been withdrawn into the body. Externally it is covered with simple cuboidal epithelium. Remnants of the allantois and yolk stalk may still be seen.

3. **Umbilical hernia.** It is caused by failure of the intestinal loop to be withdrawn into the body cavity.

II. Placentation

This includes the implantation of the early embryo in the uterine wall and the formation of the placenta.

A. Preparation of the uterus for the embryo. It is accomplished during the premenstrual (progravid) stage of the uterine cycle (p. 86), during which the endometrium undergoes changes resulting in increased vascularity, increased glandular secretions rich in glycogen, and a general loosening of the tissues of the endometrium.

B. Passage of the segmenting ovum into the uterus. When the ovum enters the uterus it is probably in the morula stage. Several days elapse before the blastocyst becomes embedded in the uterine wall. The period between fertilization and implantation is estimated at nine or ten days.

C. Implantation. The blastocyst becomes embedded in the endometrium. How this is accomplished in the human is not exactly known, but the whole process is supposed to take no more than a day. Implantation has been studied in detail in the guinea pig.

1. **Destruction of the epithelium.** Contact of the trophoblast with the uterine epithelium causes destruction of the latter, probably under the influence of trophoblastic enzymes.

2. **Invasion of the tunica propria.** After destruction of the epithelium trophoblastic processes grow into the tunica propria. The blastocyst gradually sinks into the endometrium. The orifice of entrance is closed later.

3. **Site of implantation.** It varies somewhat but it is usually at or near the fundus of the uterus on either the anterior or the posterior wall.

D. Establishment of the embryo in the endometrium.

1. Formation of embryotroph. As a result of the enzymatic activity of the trophoblast spaces are formed which contain cellular débris and some blood. This material (embryotroph) is absorbed by the trophoblast and serves as food for the embryo.

2. Hemotrophic nutrition. The rapid growth of the blastocyst after implantation results in additional destruction of the surrounding tissues. Dissolution of the walls of the capillaries and small veins leads to the formation of blood sinuses; a hemotrophic type of nutrition is thus established.

3. Primary villi. The enzymatic activities of the trophoblast are exerted only by the more superficial cells of this layer, which form syncytial projections (primary villi).

4. Secondary villi. The chorionic villi (secondary villi) are lined by the more deeply placed trophoblastic cells which are concerned with absorption of maternal nutritive substances from the blood sinuses. Hemotrophic nutrition is definitely established when branches of the umbilical vessels enter the chorion; this happens about three weeks after fertilization.

a. Differentiation of the chorionic villi. Since the umbilical vessels reach the chorion by way of the body stalk, the villi which are remote from the attachment of the latter to the chorion do not receive an abundant blood supply and gradually atrophy. The region in which they formerly occurred is the chorion laeve. The other villi continue their growth and become profusely branched (chorion frondosum).

b. Structure. Each young villus consists of a core of mesoderm containing blood vessels, enclosed within a double-layered epithelium.

(1) Syncytium. This is the outer epithelial covering consisting of a continuous layer of cytoplasm with evenly distributed nuclei. In the older villi and in the placenta at term it is represented by scattered cytoplasmic clumps containing many nuclei (syncytial knots).

(2) Langhans layer. The inner layer consists of epithelial cells (of Langhans) with definite outlines. They gradually atrophy as the villus grows, persisting only in small scattered areas.

(3) Blood vessels. The mesodermic core contains usually two

arterioles and two somewhat larger venules connected by capillaries situated mainly at the tips of the villus.

(4) Canalized fibrin. After degeneration of portions of the syncytium and of the Langhans layer the vacant spaces are occupied by depositions of fibrin. These areas of canalized fibrin increase in extent in the older placentae.

III. The Deciduae

Before describing the placenta it will be necessary to consider the changes which take place in the endometrium following implantation of the embryo. Since the endometrium is cast off after birth of the fetus it is known as the decidua. Three different regions are distinguished: The decidua vera, the decidua capsularis and the decidua basalis.

A. Decidua vera (parietalis). This is the general lining of the pregnant uterus exclusive of the region of the embryo and the cervix. Two layers are distinguished.

1. Compact layer. Contains the straight, dilated segments of the uterine glands. Its surface epithelium disappears by the end of the third (lunar) month due to contact with the decidua capsularis.

2. Spongy layer. In early pregnancy it is characterized by the greatly enlarged and tortuous portions of the uterine glands, with their long axes perpendicular to the surface of the endometrium. After the second month stretching of the decidua reduces the glands to elongated clefts parallel to the uterine surface.

3. Decidual cells. They are large, polygonal elements with one or more nuclei. Decidual cells arise from reticulo-endothelial elements which abound in the tunica propria (p. 86). They contain glycogen and are highly characteristic of pregnancy. Their function is not clearly understood.

4. Regression. The period of growth of the decidua vera is limited to the first three or four months of pregnancy; later it becomes thinner, less vascular and shows regressive changes. The decidual cells become smaller and many degenerate.

B. Decidua capsularis (reflexa). This is the endometrial portion which covers the area of implantation of the embryo. In the early stages of pregnancy it shows some of the endometrial characteristics and is covered by columnar epithelium. As the chorionic sac expands it becomes thin and atrophic. At the end of the third month

it fuses with the decidua vera and then degenerates, allowing the chorion laeve to adhere to the decidua vera.

C. Decidua basalis. Since the blastocyst is implanted superficially in the endometrium the deeper part of the compact and the spongy layer, respectively, remain intact. The two together become the basalis, which is an important part of the placenta. Decidual cells also occur in this layer.

IV. The Placenta

The placenta is a structure, part of which (chorion frondosum) is derived from the embryo (fetal placenta), the other (decidua basalis) from the mother (maternal placenta). The two portions are intimately associated into a solid, disk-shaped organ to which is attached the umbilical cord.

A. Fetal placenta. The structure of the villi of the chorion frondosum has already been described (p. 117).

1. **Cotyledons.** The villi of the frondosum are evenly distributed at first but in the older placentae become separated into 15 to 20 groups or cotyledons by the growth of trabeculae (placental septa) from the walls of the uterus.
2. **Fixation (anchoring) villi.** These are attached to the decidual wall and to the placental septa.
3. **Free villi.** In the older villous trees there are many villi which float in the cavity of the blood sinuses.
4. **Chorionic plate.** This is the portion of the chorion between the bases of the villi. It contains the larger chorionic vessels which converge in the center, where they enter the umbilical cord.
   a. **Epithelium.** The plate is lined externally by a layer of trophoblastic epithelium which rests on a layer of mesoderm.
   b. **Fusion with the amnion.** By the end of the second month the amnion is brought into contact with the chorion. In the placental area it fuses with the chorionic plate.
   c. **Production of fibrin.** During the last half of pregnancy the epithelium is replaced by canalized fibrin.

B. Maternal placenta. This is represented by the decidua basalis.

1. **Glands of the spongy layer.** They become stretched into clefts by the third month.
2. **Basal plate.** This is what remains of the compact layer of the endometrium; it is incorporated into the placenta. It consists of a

connective tissue stroma containing decidual cells, fibrinoid material and portions of the trophoblast.

3. Intervillous spaces. They arise through fusion of the blood sinuses (p. 117) during the early stages of development, following implantation. Arteries and veins open into them. The ends of the free villi float in these large spaces which are supposed to contain circulating maternal blood. This point, however, has been recently questioned.

4. Placental septa (or trabeculae). They are the septa which separate the villi of the chorion frondosum into cotyledons.

C. The placenta at term. It is convex on the uterine surface (covered by the decidua basalis) and concave on the fetal side (covered by the amnion), but after it is expelled these relations are reversed. Its margin is continuous with a membrane produced through fusion of:

1. **The decidua vera.**
2. **The decidua capsularis.**
3. **The chorion laeve.**
4. **The amnion.**

PART TWO: ORGANOGENESIS

The organs of the vertebrate body arise from the three germ layers. The endoderm gives rise to the digestive and respiratory systems. The mesoderm contributes the supporting tissues, the vascular, urogenital and muscular systems, as well as the body cavities. The ectoderm is the source of the integument, central and peripheral nervous systems, and the sense organs.

ENDODERMIC DERIVATIVES

THE DIGESTIVE SYSTEM

I. Introductory Remarks

A. Ectodermic contributions.

1. Stomodaeum. In the early embryo the fore-gut ends blindly; its endoderm is fused with the ectoderm to form the oral (pharyngeal) membrane which is the floor of an external depression, the

stomodaeum. The latter develops into the front part of the mouth and gives rise to the enamel of the teeth, salivary glands and mucosa of the nose and palate, which are, therefore, ectodermic. The oral membrane ruptures at the beginning of the 5th week.

2. Proctodaeum. The hind-gut becomes the cloaca which later is divided into the rectum and the urogenital sinus. The cloacal membrane (endoderm plus ectoderm) ruptures at the end of the 7th week. After this a short ectodermic proctodaeum is added to the rectum as its anal canal.

B. Relation to the primitive gut. The fore-gut gives rise to the posterior part of the mouth cavity, pharynx, oesophagus, stomach and a good part of the small intestine. The hind-gut forms the rest of the small intestine, colon and rectum. The intermediate region (mid-gut) is unimportant in man.

C. Pharyngeal derivatives. The endodermic lining of the pharynx gives rise to organs which in the adult have no connection with the digestive tract (thyroid, parathyroids and thymus).

II. The Organs of the Mouth Cavity

Since the tongue develops from the branchial arches it will be considered in the next section.

A. The teeth. They are the homologues of the scales of the elasmobranch fishes (i.e. products of the skin) and as such arise from two different sources: the epidermis, which forms the enamel, and a dermal papilla which is transformed into dentine and tooth pulp (dental papilla).

1. The dental lamina. This is a slightly curved epithelial ridge which sinks into the substance of the primitive gum.

2. Enamel organs. They are thickenings which develop at intervals along the lamina. Early in the 3rd month the deeper side of each organ presses against the dense accumulation of mesenchyme of the dental papilla.

a. Number. Ten enamel organs develop in each jaw. They are the primordia of the deciduous (milk) teeth.

b. Structure. The enamel organ or sac resembles an inverted cup with its concavity applied against the dental papilla.

(1) Outer enamel cells. They line the convex portion of the cup. At first cuboidal they later become flat. They do not contribute to the formation of the tooth.

(2) Inner enamel cells (ameloblasts). They line the concavity of the sac. They are columnar and secrete the enamel which covers the crown of the tooth.

(3) Enamel. Is laid down as a fibrillar layer which then calcifies in the form of elongated prisms, one for each ameloblast. It appears first at the apex of the crown and extends gradually toward the region of the future root, which it does not invest.

(4) Enamel pulp. This is derived from the epithelial elements between the outer and inner enamel cells. They are transformed into a reticulum.

c. **Nasmyth's membrane (dental cuticle).** Represents the remains of the enamel organ covering the apex of the tooth at eruption. It soon wears off.

3. **The dental papilla.** This is the mesodermic or dermal portion of the tooth.

a. **Odontoblasts.** The superficial cells (facing the ameloblasts) become the columnar odontoblasts which secrete the dentine (p. 55).

b. **Dental pulp.** The remaining mesenchyme differentiates into the dental pulp.

4. **The dental sac.** This is formed by the mesenchyme which surrounds the developing tooth. The inner portion produces a layer of osteoblasts at the level of the root; they deposit the cementum. When the tooth fills its alveolus the sac becomes the peridental membrane (p. 55).

5. **Disintegration of the dental lamina.** It occurs after the first set of enamel organs has been laid down, but its free edge gives rise to the enamel organs of the permanent teeth. A backward growth of the lamina produces the enamel organs of three molars not represented in the primary dentition.

6. **Eruption.** This is caused by growth of the root; the crown pushes to the surface and compresses the gum, which atrophies at this point.

7. **Permanent teeth.** They develop in the same way as the deciduous and lie on the lingual side of the latter. By their rapid growth at certain periods (6th to 18th year, according to the tooth) they press against the deciduous teeth, the roots of which undergo partial resorption. This causes their shedding.

B. The palate. Its development begins with the formation of the:

1. Lateral palatine processes. They are shelf-like folds of the maxillae which project toward the midline.

a. Fusion. They fuse with each other and with the greater portion of the nasal septum; the fusion begins anteriorly.

b. Formation of the hard palate. This is formed of bone which arises in the anterior part of the fused processes.

c. Soft palate. The caudal part of the processes does not unite with the nasal septum and is not ossified; this is the soft palate and its free posterior apex, the uvula, notched at first.

2. Cleft palate. Results from total or partial failure of the fusion of the lateral palatine processes. It may be associated with hare-lip (p. 112).

III. The Pharynx

The lateral walls of the embryonic pharynx form five pairs of outpocketings (pharyngeal or branchial pouches), the last of which is rudimentary in man. They come into contact with the ectoderm of corresponding branchial grooves and fuse with it, forming the closing plates, which become perforated in human embryos only occasionally.

A. The branchial arches. Their position has already been described (p. 111). They give rise to several head structures (jaws, face and external ear) and various muscles, cartilages and bones. On the floor of the pharynx they contribute to the formation of the tongue and epiglottis.

1. The tongue. The body or apical half of the organ arises in front of the second branchial arches, the root develops primarily from the second arches, but receives additions from the third and fourth. The boundary line between the body and root is the V-shaped sulcus terminalis.

a. The body. It arises from three primordia:

(1) Tuberculum impar, or median primordium present in the pharyngeal floor between the first pair of pouches. It contributes little or nothing to the formation of the human tongue, according to some authors.

(2) Paired lateral swellings, located in the mandibular arches; they meet at the median septum linguae.

b. The root. Arises from a median primordium (copula) which

is produced by the union of the second branchial arches in the midline. The adjacent portions of the arches join the copula.

c. Foramen caecum. Between the tuberculum impar and the copula is the point of origin of the thyroid diverticulum, represented by a pit (foramen caecum) in the adult.

d. Musculature. Arises from mesoderm of the floor of the mouth.

2. The epiglottis. The copula connects with a rounded prominence developed from the bases of the third and fourth branchial arches: this is the epiglottis, which becomes concave on its ventral (laryngeal) surface.

B. The pharyngeal (branchial) pouches and their derivatives. The first and second pharyngeal pouches open into broad lateral expansions of the pharynx, while the third and fourth communicate with the pharyngeal cavity through narrow canals. The different pouches give rise to a number of structures:

1. The auditory (Eustachian) tube and tympanic cavity. These arise from the first pair of pouches. Each tube is formed by a dorsal outpocketing or wing of the pouch and opens into the expanded tympanic cavity. The first branchial groove deepens as the external auditory meatus, while its closing plate becomes the ear-drum (tympanic membrane).

2. The palatine tonsils. The dorsal angle of the second pouch persists as the tonsillar fossa, which gives rise to the crypts of the palatine tonsils. (The pharyngeal and lingual tonsils are not pharyngeal pouch derivatives.)

3. The thymus. It appears as two large ventral diverticuli of the third pair of pharyngeal pouches. The corresponding diverticuli of the fourth pouches have been regarded as rudimentary thymic primordia which usually atrophy.

a. Loss of the lumina. The diverticuli become solid epithelial masses and lose their connection with the wall of the pouch.

b. Fusion. The fusion of the epithelial masses in the midline is superficial and produces the body of the gland, which gradually takes its permanent position in the thorax.

c. Formation of the reticulum. The epithelium is changed into a reticular framework through formation of large cytoplasmic vacuoles. The Hassal bodies are supposed to arise from this endodermic reticulum.

d. Invasion by lymphocytes. Takes place toward the end of the 3rd month when the organ begins its differentiation into cortex and medulla.

4. The parathyroids. They arise from the dorsal diverticuli of the third and fourth pharyngeal pouches and, accordingly, are designated as parathyroid III and IV, respectively.

a. Migration. They leave the pouches in the 7th week and migrate caudad.

b. Permanent position. Parathyroids III are dragged downward by the thymic primordia so that they come to lie at the caudal thyroid border, while parathyroids IV are nearer the cranial border.

5. The ultimobranchial bodies. Usually regarded as derived from the fifth pouches, they leave their site of origin and migrate caudad with parathyroids IV, fusing with the thyroid. Their ultimate evolution varies according to the species; in man it is claimed that they give rise to thyroid tissue.

C. The thyroid gland. It develops as a diverticulum arising from the floor of the pharynx.

1. Thyro-glossal duct. The thyroid diverticulum is connected with the pharyngeal epithelium through this duct which, if persistent, opens in the foramen caecum of the tongue. It usually atrophies during the 6th week.

2. Loss of the lumen. The body of the diverticulum becomes bilobed and through loss of its lumen is converted into a solid structure composed of epithelial plates.

3. Formation of follicles. Cavities representing the follicles begin to appear in the epithelial plates; they soon acquire colloid. This process ends by the end of the 4th month.

IV. The Digestive Tube

The development of its different regions is rather uniform except for such differences as size, shape and position. The epithelial lining is endoderm invested by splanchnic mesoderm; the latter gives rise to the other layers.

A. Oesophagus. Its development is characterized by a gradual differentiation of the walls.

B. Stomach. In early embryos it is a spindle-shaped dilatation of the gut.

1. Formation of the curvatures. The dorsal border grows faster than the ventral and this unequal growth causes the formation of the greater curvature. The fundus arises as a sacculation near the cardia.

2. Mesenteries. The dorsal mesogastrium grows faster than the ventral; it forms the omental bursa (p. 129).

3. Rotation. The stomach rotates about its long axis until the greater curvature lies on the left and the lesser (primitive ventral border) is on the right.

C. Intestine. In early embryos the intestine forms a single loop which enters the coelomic extension of the umbilical cord. Later the caudal limb of the loop develops a swelling which indicates the caecum, and the loop is withdrawn into the body cavity.

1. Torsion. This takes place about the superior mesenteric artery in such a way that the cranial limb of the loop is carried to the right and caudad of the caudal limb; the latter shifts to the left and cephalad.

2. Elongation and formation of loops. Rapid growth of the small intestine causes the formation of its characteristic loops. The first of these is the duodenum.

3. Differentiation of the colon. The formation of the three portions of the colon is a complicated process and will not be described here.

V. The Liver

It first appears as the hepatic diverticulum which is an outpocketing of the ventral floor of the fore-gut.

A. Penetration into the ventral mesentery. Ventral growth of the hepatic diverticulum causes its penetration into the splanchnic mesoderm of the ventral mesentery; the latter is split into halves which encapsulate the liver, forming the capsule of Glisson.

B. Formation of the hepatic cords. Soon after the formation of the diverticulum its blind end produces solid anastomosing cellular cords which constitute the parenchyma of the liver.

C. Formation of the sinusoids. The hepatic diverticulum lies between the vitelline (ophalomesenteric) veins, which form plexuses in the ventral mesentery. The epithelial cords grow between these venous plexuses which become the sinusoids.

D. Ducts. The hepatic duct and the common bile duct (ductus choledochus) are the stem portions of the original hollow hepatic

diverticulum, while the gall bladder and cystic duct represent a secondary, more caudally placed outpocketing.

VI. The Pancreas

The pancreas arises from two primordia (dorsal and ventral), which are outpocketings of the endoderm lining the duodenum.

A. Dorsal pancreas. It extends into the mesentery as a solid cell mass connected with the duodenum by a duct.

B. Ventral pancreas. This remains smaller and its short duct is dragged away from the duodenum by the common bile duct, from which it secondarily arises.

C. Fusion of the primordia. The primordium of the ventral pancreas is shifted to the dorsal mesentery near the dorsal pancreas with which it fuses completely. It forms the head of the organ.

D. Ducts. The distal segment of the dorsal duct fused with the entire ventral duct form the main pancreatic duct (of Wirsung). The proximal segment of the dorsal duct becomes the accessory duct (of Santorini).

THE RESPIRATORY SYSTEM

The respiratory system (except the nasal passages) arises as an outpocketing or evagination of the ventral wall of the fore-gut

I. Early Development

A. The laryngo-tracheal groove. It appears in very early embryos along the floor of the fore-gut, caudal to the pharyngeal pouches. It becomes the larynx and trachea.

B. Lung buds. The rounded, posterior end of the groove projects ventrally and represents a single primordium of the lungs. It splits caudally into two outpocketings, the lung buds, which remain connected with the future trachea.

C. Tracheo-oesophageal grooves. They form on the lateral aspects of the fore-gut; their deepening toward the midline and subsequent fusion cause the separation of the trachea from the oesophagus.

II. The Larynx

A. Arytenoid swellings. They bound laterally the upper end of the laryngeal portion of the laryngo-tracheal groove.

1. Fusion with the epiglottis. Through fusion with the epiglottis

the arytenoid swellings produce a U-shaped ridge, the furcula. The fusion is temporary, however.

2. **Bending.** The parallel swellings are bent at the middle so that their cranial positions diverge laterally, nearly at right angles to their caudal portions.

3. **Formation of the glottis.** When the arytenoid swellings lose contact with the epiglottis the entrance to the larynx—previously T-shaped and obliterated through fusion of the epithelial lining—becomes oval and patent.

B. Development of the laryngeal cartilages and muscles. They arise from condensations of mesenchyme derived from the fourth and fifth pairs of branchial arches (p. 150).

III. The Trachea

Its development is mainly represented by elongation and the differentiation of its walls.

IV. The Lungs

The right lung bud soon becomes larger and is directed caudad.

A. Bronchial buds. The right lung bud gives off two lateral bronchial buds, the left only one.

1. **Relation to the lobes.** The bronchial buds indicate the position of the upper and middle lobes on the right side, the upper lobe on the left. The lower lobes arise from the blind ends of the lung buds.

2. **Eparterial bronchus.** This is the apical bronchus of the right upper lobe, so called because it alone passes dorsal to the pulmonary artery.

3. **Cardiac bronchus.** This is the ventral bronchus of the right lower lobe, which in a way compensates for the loss of a corresponding branch of the left side, eliminated so as to make room for the heart.

4. **Branching of the buds.** The bronchial buds branch repeatedly, and their epithelium becomes lower; in the terminal portions (pulmonary alveoli) it is actually flattened. The existence of alveolar epithelium, however, is questioned by some (p. 69).

B. Development of the lobes. The respiratory tree develops in a median mass of mesenchyme which resembles a broad mesentery and is later called the mediastinum.

1. Invasion of the pleural cavities. The developing lungs, invested by a layer of mesoderm, grow out laterally into the pleural cavities. The branching of the bronchial buds takes place within this mesoderm, and the external lobation becomes apparent.

2. Differentiation of the mesoderm. The mesenchyme surrounding the bronchial tree produces the tissues of the wall of the bronchi.

3. Visceral and parietal pleura. The surface of each developing lung is covered with mesoderm lined externally by mesothelium; this is the visceral pleura. The corresponding layer lining the thoracic wall is the parietal pleura.

C. The lungs at birth. Until birth the lungs are small and compact and do not fill the pleural cavities. With the onset of breathing they gradually distend with air and the lung tissue becomes light and spongy.

MESODERMIC DERIVATIVES

THE MESENTERIES AND COELOM

I. The Mesenteries

Soon after it is formed the primitive gut is enclosed into a mesentery, which arises through fusion of the splanchnic mesoderm of the two sides in the midline. The gut subdivides this primitive mesentery into dorsal and ventral halves.

A. The dorsal mesentery. The pharynx and upper oesophagus have no mesentery; the lower oesophagus, like the trachea, lies in the future mediastinum. The rest of the digestive tract is suspended from the dorsal body wall by a continuous mesentery.

1. Regional names. The portion which attaches the stomach to the dorsal body wall is the dorsal mesogastrium or greater omentum; then there is a mesoduodenum, mesentery of the small intestine, mesocolon and mesorectum.

2. The formation of the omental bursa. The lengthening and bending of the dorsal mesogastrium toward the left during rotation of the stomach (p. 126) forms the omental bursa. In young embryos (up to 10 mm.) the bursa is bounded mesially by the dorsal mesogastrium (greater omentum) and the right wall of the stomach, laterally by the right lobe of the liver and the mesen-

tery in which the hepatic portion of the inferior vena cava develops (caval mesentery).

a. Epiploic foramen (of Winslow). The bursa communicates to the right with the vestibule; the latter opens into the peritoneal cavity through this foramen situated between the liver and the caval mesentery.

b. The inferior recess. This is due to enlargement of the bursa to the left and caudad. Posteriorly it ends blindly.

c. Fusion with the dorsal body wall and colon. The dorsal wall of the bursa fuses with the dorsal body wall as well as with the colon and its mesentery (mesocolon).

d. Obliteration of the inferior recess. Its anterior and posterior walls fuse. In the adult it is reduced to a space between the stomach and dorsal fold of the greater omentum, the latter being largely fused with the dorsal body wall.

3. Secondary fusions of the dorsal mesentery. They occur as the result of the upright position in man and the higher apes. The most important leads to the formation of the transverse mesocolon and fixes the duodenum and pancreas to the dorsal body wall.

B. The ventral mesentery. It is associated intimately with the development of the heart and liver. The portion between the liver, stomach and duodenum is the lesser omentum. The greater part of the ventral mesentery disappears early and the right and left peritoneal cavities merge into a single cavity. What remains gives rise to the falciform and coronary ligaments of the liver.

II. The Coelom (Body Cavity)

In early embryos the two halves of the coelom merge into a single cavity in front as well as ventral to the heart, but caudal to the latter the two coelomic cavities remain independent. The coelom can be compared with an inverted U; the bend is occupied by the pericardial cavity, while the limbs represent the pleuro-peritoneal canals.

A. Division into separate cavities. The separation of the pericardium, pleural cavities and peritoneal cavity is effected by the development of three sets of partitions.

1. The septum transversum. This is located caudal to the heart and fills the space between the gut, yolk stalk, and ventral body wall, separating the pericardial and peritoneal cavities.

a. **Pleuro-pericardial canals.** Since the septum does not extend dorsal to the gut it leaves on each side a canal through which the pericardial and peritoneal cavities communicate.

b. **Migration.** The septum, at first in the cervical region, undergoes a gradual displacement caudad. The permanent location is reached in the two-month embryo.

2. **Pleuro-pericardial membranes.** They separate the pleural cavities from the pericardial cavity; they develop around the common cardinal vein of each side.

3. **Pleuro-peritoneal membranes.** These gradually separate the pleural cavities and the single peritoneal cavity.

B. **The diaphragm.** The partitioning of the coelom results in the formation of the diaphragm.

1. **Origin.** The diaphragm of the adult is derived from four sources:

a. Its ventral portion from the septum transversum.

b. Its lateral parts from the pleuro-peritoneal membranes, and:

c. Derivatives from the body wall.

d. The median dorsal portion is contributed by the dorsal mesentery.

2. **Diaphragmatic hernia.** Since the diaphragm arises from multiple sources, imperfect development or absence of one of them leads to this defect, which is more common on the left side due to failure of the formation of the pleuro-peritoneal membrane.

THE VASCULAR SYSTEM

I. Origin of the Blood and Hemopoiesis in the Embryo

The blood and the blood vessels first appear in the splanchnic mesoderm that invests the yolk sac.

A. **Blood islands.** These are solid masses of cells which are soon changed into vesicles.

1. **Formation of the endothelium.** The peripheral cells of the blood islands are arranged into a single layer of flattened cells, which may also arise from the surrounding mesenchyme.

2. **Blood cells.** The other cells in the island become erythrocytes.

3. **Plasma.** It accumulates within the island and separates the blood cells, which thus float in it.

B. Area vasculosa. This is a network of primitive vessels in the wall of the yolk sac. It arises through fusion of the blood islands.

C. Embryonic vessels. The first vessels to appear within the embryo proper arise as clefts within the body mesenchyme.

D. Sites of hemopoiesis. The formation of blood takes place in the following locations:

1. **The yolk sac** (4th week).
2. **Body mesenchyme and blood vessels** (5th week).
3. **Liver sinusoids** (6th week).
4. **Spleen, lymph nodes and thymus** (2nd to 3rd months).
5. **Bone marrow,** from 3rd month on throughout postnatal life. (For hemopoiesis in postnatal life see p. 10.)

II. The Early Vascular System

The embryonic vessels arise through coalescence of the vesicles in which the blood develops. The first paired vessels to appear are the:

A. Aortae. They run anteriorly under the fore-gut (ventral aortae) and bend dorsally in front of its blind end to become the dorsal aortae. The latter soon fuse into a single descending aorta.

B. Cardiac tubes. The short ventral aortae are connected posteriorly with the cardiac tubes, which later fuse into a single heart.

C. Umbilical arteries. The dorsal aorta give off caudally these two vessels which enter the body stalk on their way to the chorion.

D. Umbilical veins. These course in the body wall and return the blood from the chorion to the heart.

E. Vitelline vessels. They are: a pair of vitelline arteries arising from the dorsal aorta and ending in the area vasculosa of the yolk sac, and a pair of vitelline veins opening into the heart.

F. Embryonic veins. They arise within the body of the embryo.

1. **Anterior cardinal (precardinal) veins.** They drain the blood from the head region; they course in the somatopleura.
2. **Posterior cardinal (postcardinal) veins.** They return the blood from the posterior end of the body.
3. **Common cardinals (ducts of Cuvier).** Before entering the heart the two cardinals of each side form this common trunk which crosses the pleuro-peritoneal canal.

G. Aortic arches. They connect the ventral with the dorsal aortae.

The first pair is the anterior bend of the ventral aorta as it becomes dorsal; four more pairs develop more caudally (p. 136).

III. Development of the Heart

The heart arises through fusion of paired primordia (cardiac tubes) just posterior to the ventral aortae.

A. Early development.

1. Fusion into a single tube. This is caused by the process of folding which gives rise to the fore-gut. The single cardiac tube has an endothelial lining.

a. Dorsal mesocardium. The cardiac tube is suspended from the dorsal body wall by this double sheet, formed by fusion of the two plates of splanchnic mesoderm in the midline. It soon disappears.

b. Ventral mesocardium. This develops in the chick embryo but it is absent in the mammal due to the precocious splitting of the mesoderm.

c. Epi-myocardium. The layer of thickened splanchnic mesoderm that surrounds the endothelial tube and gives rise to the epicardium and myocardium.

2. Division into regions. The single cardiac tube soon shows the following regions:

a. The sinus venosus, which receives the blood from the umbilical, vitelline and common cardinal veins; it develops a pair of valves which guard the opening into:

b. The atrium, placed anteriorly to the sinus and communicating with:

c. The ventricle through a narrow atrio-ventricular canal.

d. The bulbus, continuous with the short ventral aortae.

B. External changes. They result from the bending of the single cardiac tube, which grows in length faster than the cavity in which it is contained.

1. Bulbo-ventricular loop. This chief early flexure is to the right, and it has the shape of a U; one limb is the bulbus, the other the ventricle.

2. Formation of the atria. Due to growth of the bulbo-ventricular loop the atrium and sinus venosus shift cephalad. The single atrium forms lateral outpocketings which become the paired atria; the furrow between them is the interatrial sulcus.

3. **Formation of the primitive ventricle.** With continued growth of the bulbo-ventricular loop its two limbs become confluent: the single chamber is the primitive ventricle, separated from the atria by the deep coronary sulcus.

4. **Interventricular sulcus.** This is the external manifestation of the formation of the interventricular septum, which separates the two ventricles.

C. **Internal changes.** They lead to the formation of the four-chambered heart characteristic of birds and mammals.

1. **Development of the atria.** The partitioning of the atria is a gradual process which is not completed until after birth.

a. **Septum primum.** At first it is a sickle-shaped partition that grows from the mid-dorsal atrial wall: it advances toward the ventricle and its free edge fuses with the endocardial cushions (p. 136), which have split the primitive atrio-ventricular canal into right and left halves.

(1) Foramen interatriale primum. This is the space enclosed within the concavity of the septum: before the latter finally reaches the endocardial cushions a secondary perforation occurs, the:

(2) Foramen interatriale secundum (ovale I), which is located near the attachment of the septum to the dorsal atrial wall.

b. **Septum secundum.** It makes its appearance just to the right of the septum primum. It arises from the caudal end of the left valve of the sinus venosus (p. 135). It is also sickle-shaped; its concavity is the:

(1) Foramen ovale (ovale II), which never disappears as such and becomes the oval fossa of the adult heart.

(2) Relation of the foramen ovale II to the septum primum. Since the foramen ovale II is placed more ventrally than the interatriale secundum (ovale I), it is overlapped by the imperforated portion of the septum primum.

(3) Passage of the blood through the foramen ovale. The portion of the septum primum covering the foramen ovale II serves as a flap-like valve permitting passage of the blood from the right to the left atrium, but not in the reverse direction.

c. **The atrial septum.** It arises after birth through fusion of the

edges of the septum secundum with the septum primum. The edge of the former becomes the limbus of the oval fossa, the septum primum the membranous portion of the fossa. This fusion closes the foramen.

2. The sinus venosus. The sinus venosus soon develops a large right and a smaller left horn. The horns receive the blood returning to the heart through the primitive embryonic veins (p. 132).

a. The right horn. After their formation (p. 139), the superior and inferior vena cava open into the right horn. Rapid atrial growth incorporates the horn into the wall of the right atrium, and the venae cavae open directly into the latter.

b. The left horn. It becomes the coronary sinus.

c. Transformations of the valves. The opening of the sinus venosus into the atrium is guarded by two valves (valvulae venosae). The left valve is incorporated into the septum. The right forms the:

(1) Crista terminalis, which is a continuation of its cephalic portion: and the:

(2) Eustachian and Thebesian valves, which arise from the remainder of the valve. The former (valve of the inferior vena cava) is larger than the Thebesian (valve of the coronary sinus).

3. The pulmonary veins. The single pulmonary vein of the early embryo splits into right and left branches which in turn bifurcate. During the rapid growth of the atria first the single stem, then its two branches of bifurcation, are incorporated into the atrial wall, and the four branches (two for each lung) come to open directly into the atrium.

4. Origin of the aorta and pulmonary artery. They arise early in embryonic life through division of the aortic bulb (bulbus, p. 133). This is accomplished by two lateral ridges which meet and fuse in the midline.

a. Relative position. After they are formed, the two arteries are not parallel but arranged somewhat like an X; the more ventral of the two is the pulmonary artery, the other the aorta (crossing toward the right dorsal to the pulmonary).

b. Aortic and pulmonary valves. They arise from endocardial thickenings of the aortic bulb.

5. The ventricles. The ventricles are lateral outpocketings of the

early single ventricle. Their separation is accomplished by the formation of the:

a. **Interventricular septum,** which arises at the time of division of the aortic bulb, as a median elevation extending to the ventral endocardial cushion.

b. **Interventricular foramen.** This is a temporary communication between the right and left ventricles.

c. **Septum membranaceum.** It closes the interventricular foramen and completes the partition of the single ventricle.

6. **The atrio-ventricular valves.** They arise from the endocardial cushions which by fusion convert the single atrio-ventricular canal into two canals. Endocardial folds at the margins of these canals form the flaps of the valves, which become attached to the muscular trabeculae of the inner ventricular wall.

D. Anomalies. They are rather frequent. Among the most important are:

1. **Dextrocardia,** or transposition of the heart, usually associated with general inversion of the viscera (situs inversus).

2. **Incomplete ventricular septum** due to deficiency of the septum membranaceum.

3. **Persistence of the foramen ovale** due to improper fusion of the septum primum and secundum. When the blood of the two sides mixes it causes cyanosis, seen in the "blue baby."

IV. Development of the Arteries

The first arteries to appear in the embryo have already been mentioned, as well as the presence of aortic arches. The transformations of the latter are of great importance.

A. Transformation of the aortic arches.

1. **Number of arches.** In human embryos there are five pairs of aortic arches, which are numbered first, second, third, fourth and sixth since the fifth, present in other animals, never develops fully. They are not all present at any one time, due to early degeneration of the first and second.

2. **Internal carotids.** They are cephalic portions of the dorsal aortae after the disappearance of the first and second arches. They continue growing cephalad to enter the head.

3. **External carotids.** Each arises from the third arch, the proximal part of which becomes the common carotid. The distal part of

the arch joining with the dorsal aorta becomes the proximal segment of the internal carotid.

4. **Fourth arches.** They also persist.

a. **Left side.** It becomes the arch of the aorta. Proximally, the short left ventral aorta is added to it.

b. **Right side.** The fourth arch arises from the enlarged right ventral aorta (now called the innominate) and constitutes the proximal part of the right subclavia. The middle part of the latter is the portion of the left aorta between the fourth arch and the vicinity of the point of fusion of the two aortae, while the distal part is a new growth arising from the caudal end of the middle portion at the level of the limb bud.

5. **Left subclavia.** This springs directly from the left dorsal aorta at the level of the corresponding limb bud but its position is shifted cephalad in later stages of development.

6. **Sixth (pulmonary) arches.** They arise from the pulmonary artery after its separation from the aorta (p. 135) and connect with the dorsal aortae.

a. **Right side.** A branch entering the corresponding lung bud arises about the middle of the arch. The portion of the latter between the origin of the branch and the right aorta degenerates.

b. **Left side.** A similar branch for the left lung bud is given off, but the portion of the arch between the branch and the left aorta remains as the:

c. **Ductus arteriosus (Botalli)** which becomes the arterial ligament of the adult.

B. **Branches of the dorsal aorta.** The aortae give off dorsal, lateral and ventral branches. The most important of each are:

1. **Dorsal (intersegmental) arteries.**

a. **Vertebral artery.** It arises from the subclavia. The two vertebrals join under the brain with the basilar artery.

b. **Intercostal and lumbar arteries.** They are the ventral rami of the dorsal intersegmental arteries.

2. **Lateral arteries.** They give rise to the renal, suprarenal, inferior phrenic and internal spermatic and ovarian arteries.

3. **Ventral branches.** The most important are the vitelline, coeliac, superior and inferior mesenteric, and the paired umbilicals.

V. Development of the Veins

The first paired veins to develop are the vitelline, umbilical and cardinals (p. 132). They undergo a series of transformations leading to the venous plan of the adult.

A. The vitelline (omphalomesenteric) veins. Their course is interrupted by growth of the liver which divides them into a large number of sinusoids. Each vein has a distal segment (from the yolk sac to the liver) and a proximal (from the liver to the corresponding horn of the sinus venosus).

1. **The hepatic veins.** They arise from the proximal parts of the vitelline veins.
2. **Fate of the distal segments.** They communicate with each other by three transverse anastomoses: a cranial (within the liver) and two dorsal and ventral to the duodenum, respectively. The more cranial portion of the left vitelline (within the liver) and the middle portion of the right drop out. What remains is shaped like an S.
   a. **Formation of the superior mesenteric.** This is a new vessel which develops in the mesentery of the intestinal loop and joins the left vitelline vein near its middle anastomosis.
   b. **The portal vein.** The persisting portion of the left vitelline vein and the portion of the right between the middle and cranial anastomosis become this vessel.

B. The umbilical veins. As the liver expands, its lateral surfaces engulf the umbilicals, which then send their blood to the heart by the more direct route of the liver sinusoids.

1. **Fate of the right umbilical.** When all the umbilical blood enters the liver the entire right umbilical vein atrophies.
2. **Left umbilical.** Its proximal segment also atrophies.
3. **Formation of the ductus venosus.** This arises through enlargement of some of the hepatic sinusoids. It communicates with the left umbilical and opens into the common hepatic vein.
4. **Fate of the ductus venosus.** After birth it is obliterated and forms the solid venous ligament.
5. **Fate of the left umbilical vein.** Through a similar obliteration its remnant, from the navel to the liver, constitutes the ligamentum teres.

C. The cardinal veins.

1. **Anterior cardinals.** An oblique anastomosis between these veins gives rise to the:

   a. **Left innominate vein,** which increases in diameter as the proximal portion of the left cardinal atrophies.

   b. **Superior vena cava.** The right common cardinal and anterior cardinal as far as the oblique anastomosis become the superior vena cava.

   c. **Right innominate vein.** The portion of the right anterior cardinal between the anastomosis and the right subclavian.

   d. **Internal jugulars.** They are the distal segments of the anterior cardinals.

   e. **External jugulars and subclavian veins.** They develop independently and later open into the anterior cardinals.

2. **Posterior cardinals, subcardinals and supracardinal veins.** These three sets of veins appear successively in the order mentioned.

   a. **Postcardinals.** They develop primarily as the veins of the mesonephroi and disappear as these organs wane.

   b. **Subcardinals.** They anastomose in the midline; the anastomosis forms the left renal vein.

   c. **Supracardinals.** They unite by a transverse anastomosis and become the azygos and hemiazygos veins.

3. **The inferior vena cava.** It consists of four segments arising from different sources:

   a. **An hepatic segment,** derived from the hepatic vein and sinusoids; it connects with the right subcardinal through a vein in the caval mesentery (p. 130).

   b. **A prerenal segment,** formed from the right subcardinal.

   c. **A renal segment,** comprising an anastomosis between the right subcardinal and right supracardinal veins.

   d. **A supracardinal segment,** from the lumbar portion of the right supracardinal vein.

VI. Fetal Circulation and Changes at Birth

A. Course followed by the blood in the fetus. Contrary to formerly held views the oxygenated blood reaching the fetus through the umbilical vein becomes mixed with venous blood from diverse sources.

1. **Source of the oxygenated blood.** This is the placenta, where the

venous blood conveyed to the chorionic villi by the umbilical arteries becomes arterial.

2. **Return of the oxygenated blood.** By way of the left umbilical vein it enters the ductus venosus and reaches the right atrium through the inferior vena cava.

3. **Mixing of the blood.** The venous blood of the portal vein and inferior vena cava contaminates the oxygenated blood; a further mixture of bloods takes place in the right atrium, which receives venous blood through the superior vena cava.

4. **Passage through the heart.** The mixed blood which has entered the right atrium follows two different courses:

   a. **Through the foramen ovale** to left atrium, and through the aorta to the head and body.

   b. **Through the right atrio-ventricular foramen** to the right ventricle and hence to the aorta through left pulmonary artery and ductus arteriosus.

B. Changes at birth. The placental circulation ceases when the lungs become functional. The chief events following this change are:

1. **Gradual closure of the foramen ovale** (p. 134) resulting from equalization of the pressures in the two atria.

2. **Obliteration of the ductus arteriosus** (p. 137) following increased diversion of blood from the pulmonary trunk to the lungs.

3. **Rapid obliteration of the umbilical vein,** whose fate has been indicated (p. 138). The arteries become the lateral umbilical ligaments.

4. **Atrophy of the ductus venosus,** and its transformation into the ligamentum venosum.

THE UROGENITAL SYSTEM

The urinary and reproductive systems are closely associated in development. Both arise from mesoderm of the same region as a common urogenital fold which is soon divided into nephric and genital ridges.

I. The Urinary Organs

In the course of evolution the vertebrates have developed three types of kidneys: the pronephros, present in Amphioxus and certain lampreys; the mesonephros, functional throughout life in fishes

and amphibians; and the metanephros or definitive kidney of reptiles, birds and mammals. The three types occur in a sequence during the development of the higher vertebrates.

A. Pronephros. In the human it consists of about seven pairs of rudimentary tubules.

1. Origin. They are formed as dorsal outpocketings of the intermediate cell mass (nephrotome) of the 7th to 14th somites. The first formed tubules degenerate before the last appear.

2. Pronephric ducts. The tubules of each side open into a longitudinal collecting tube which reaches the lateral wall of the cloaca, in which it opens.

B. Mesonephros (Wolffian body). This is larger than the pronephros and serves as a temporary excretory organ. It is constituted by many tubules (up to 80) which arise cranially as far as the 6th cervical segment.

1. Differentiation of the tubules. The free end of the early S-shaped tubule is dilated, and its walls become thin. The proximal end is united with the pronephric (now mesonephric) duct.

a. Formation of the glomeruli. A knot of looped blood vessels pressing on one of the hemispheres of the dilated portion causes its invagination into the other hemisphere.

b. Bowman's capsule. This is the double-walled capsule produced by the invagination mentioned above. The capsule and glomerulus together constitute a mesonephric (Malpighian) corpuscle.

c. Tubular portion. Each tubule shows a light staining secretory portion and a thinner, more deeply stained collecting part opening into the mesonephric duct.

d. Position. The glomeruli are mesially placed, the ducts occupy a lateral position while the tubules are largely dorsal.

C. Metanephros (permanent kidney). This arises in the pelvic region and it has a double origin. The ureter, pelvis and collecting tubules are outgrowths of the mesonephric duct; the secretory tubules and glomeruli develop from the caudal end of the nephrogenic cord.

1. The ureteric bud. This arises from the mesonephric duct; it grows at first dorsad, then turns cephalad. Its proximal, elongated portion is the ureter, the distal expanded portion the renal pelvis.

2. Formation of collecting tubules. These grow out from the

primitive renal pelvis. Through branching they give rise to secondary, tertiary, quaternary, etc., tubules until about 12 generations have been produced; the tubules of the 5th order become papillary ducts (p. 72). The collecting tubules form a large part of the medulla.

3. **Differentiation of the nephrogenic blastema.** This forms a cap about the primitive pelvis and is carried along with it during the elongation of the ureteric bud.

a. **Formation of the lobes.** The nephrogenic blastema covers the ends of the newly formed collecting tubules tributary to a primary tubule; in this way the cortex is subdivided into lobes by grooves. The external lobation gradually disappears after birth.

b. **Formation of the secretory tubules.** They arise from the blastema. The first few generations degenerate; new ones are produced near the surface of the organ.

4. **Union of the secretory and collecting portions of the tubules.** They unite secondarily into continuous tubules. Failure of this union leads to congenital cystic kidney.

D. **Differentiation of the cloaca.** In early human embryos the cloaca receives laterally the mesonephric ducts, dorsally the hind-gut, while its cephalic end gives off the allantois.

1. **Division.** It is accomplished through the development of the cloacal septum which, pushing caudad, separates the dorsal rectum from the ventral urogenital sinus.

2. **Primitive perineum.** This is the exposed tip of the septum, after rupture of the cloacal membrane (p. 121) which it reaches.

3. **Differentiation of the urogenital sinus.** By elongation and constriction the sinus is divided into:

a. **The vesico-urethral portion,** which receives the mesonephric ducts and ureters and is continuous with the allantois.

b. **The phallic portion,** connected with the former by a narrow constriction and extending into the genital tubercle of both sexes (p. 147). It becomes the cavernous urethra of the male but it is merely merged with the vaginal vestibule of the female (p. 147).

4. **Differentiation of the vesico-urethral portion.** The enlarging bladder takes up into its walls the proximal ends of the meso-

nephric ducts to a level beyond the origin of the ureters; the four ducts thus acquire separate openings.

a. **The ureters,** open more laterally into the saccular bladder.

b. **The mesonephric ducts** are displaced caudad and come to open into the dorsal wall of the urethra on a hillock (Müller's tubercle).

c. **Urachus.** This is the apex of the bladder continuous with the allantoic stalk at the umbilicus; after birth it constitutes the middle umbilical ligament.

II. The Genital Organs

The early development of the genital organs is identical in the two sexes. Each embryo develops a male and female system of ducts; after the sex is definitely established the ducts of the opposite sex degenerate.

A. **The gonads.** This term is applied to the primordial sex glands during their early indifferent stage.

1. **Origin.** They arise from the genital fold, which separates from the mesonephric fold in early phases of development.

2. **Structure.** The indifferent gonad consists of:

a. **The germinal epithelium,** of cuboidal cells forming one or more layers.

b. **An inner epithelial mass** of anastomosed strands derived from the germinal epithelium. The cords are separated by mesenchyme and contain scattered germ cells.

B. **Differentiation of the testis.** This happens after the 6th week.

1. **The testis cords.** These are branched and anastomosed strands proliferated from the germinal epithelium. They consist of indifferent cells with a few larger germ cells.

2. **The albuginea.** It arises from mesenchyme that penetrates between the germinal epithelium and the testis cords.

3. **Fate of the germinal epithelium.** It is changed into ordinary mesothelium.

4. **The rete testis.** The testis cords converge toward the mesorchium and connect with the dense primordium of the rete testis.

5. **The seminiferous tubules.** The cord cells gradually arrange themselves as a stratified epithelium lining lumina continuous with the lumina of the rete. Spermatogonia arise from indifferent

cells. The proximal portions of the tubules remain straight (tubuli recti).

C. **Differentiation of the ovary.** The differentiation of the ovary takes place later than in the case of the testis.

1. **Division into cortex and medulla.** The inner epithelial mass of the indifferent gonad becomes less dense centrally to produce the medulla, while near the periphery it constitutes a denser cortex. Primordial germ cells occur in both zones, but they predominate in the medulla.

2. **The rete ovarii.** This is the homologue of the rete testis and arises from a dense primordium.

3. **The second proliferation.** After the 3rd month the ovary grows rapidly, owing to the formation of a new cortex probably derived through proliferation of the germinal epithelium.

4. **The albuginea.** After the second proliferation the albuginea differentiates beneath the germinal epithelium, which does not become mesothelium but remains as a layer of cuboidal or low columnar cells (p. 81).

D. **Transformation of the mesonephric tubules and ducts.** The involution or degeneration of the mesonephros spares a number of mesonephric tubules, which remain connected with the sex glands in the two sexes. They form a cranial and a caudal group.

1. **In the male.**

a. **Cranial group.** Most of the cranially placed tubules (9 to 15) become connected with the tubules of the rete testis to form the ductuli efferentes, but a few of the most cranially placed form the appendix of the epididymis.

b. **Caudal group.** This, although composed of vestigial tubules, persists as the coiled, blindly ending tubules of the paradidymis, and the aberrant ductules.

c. **Mesonephric duct.** Its upper end coils into the duct of the epididymis, while the caudal portion remains straight and extends from the epididymis to the urethra as the ductus deferens and ejaculatory duct.

d. **Ampulla.** It develops near the opening of the ejaculatory duct into the urethra; the seminal vesicle is an outpocketing of the ampulla.

2. **In the female.** Although the rete ovarii is vestigial it is retained in the adult.

a. Cranial group. Most tubules of this group form the epoöphoron, but a few, cranially placed, become the cystic vesicular appendages associated with the fimbria; they are the homologues of the efferent ductules and appendix of the epididymis.

b. Caudal group. They constitute the more inconstant paroöphoron, the homologue of the paradidymis and ductuli aberrantes of the male.

c. Mesonephric duct. Its greater part atrophies; the persisting portions are the ducts of the paroöphoron (Gartner's ducts) present in the region of the uterus and vagina; they correspond to the duct of the epididymis, ductus deferens, seminal vesicle and ejaculatory duct of the male.

E. The Müllerian ducts.

1. Origin. They first appear as a ventro-lateral groove in the thickened epithelium of each urogenital fold, near the cephalic pole of the mesonephros.

2. Closure of the groove. The cranial end of the groove remains open, while the rest closes into a tube which separates from the epithelium, beneath which it comes to lie.

3. Opening into the cloaca. The solid end of the tube grows caudad, beneath the epithelium and lateral to the mesonephric duct. The tubes meet in the midline and penetrate the dorsal wall of the uro-genital sinus, along with the mesonephric ducts.

4. Fate in the two sexes.

a. In the female.

(1) Uterine (Fallopian) tubes. They arise from the cranial portions of the ducts.

(2) Uterus. This originates from the next portion of the ducts, which fuse into a single tube. The thick muscular walls of the uterus are foreshadowed by the presence of a thick layer of mesenchyme around the epithelial portions of the tubes.

(3) Vagina. The upper two thirds are probably formed through fusion of the Müllerian ducts in the midline. The lower third arises from the uro-genital sinus.

b. In the male. Degeneration of the Müllerian ducts begins with the third month and only the extreme cranial and caudal ends are spared.

(1) Cranial end. It becomes the appendage of the testis.

(2) Caudal end. It persists as a small pouch on the dorsal wall of the urethra, the utriculus prostaticus or masculine vagina.

F. Descent of the testis and ovary. Their original positions gradually change during development. At first they extend caudad from the diaphragm, but later they are shifted to a more caudal position.

1. Testes. Their caudal ends come to lie at the boundary between abdomen and pelvis. This early migration is followed by their descent into the scrotal sacs.

a. Formation of the vaginal processes. These arise early in the third month. Each is an outpocketing of the abdominal cavity which passes over the pubis, then through the inguinal canal into the corresponding scrotal sac.

b. The gubernaculum testis. A continuous ligament extending from the caudal end of the testis through the inguinal canal to the scrotal integument.

c. Penetration into the scrotal sacs. During the 8th month shortening of the gubernacula draws the testes into the scrotum. Each testis is still retro-peritoneal (i.e. it is covered by the wall of the processus vaginalis) so it lies outside the cavity of the latter. Failure of the testis to enter the scrotal sac causes cryptorchism.

d. Obliteration of the canal of the vaginal process. After birth this narrow canal, connecting the vaginal process with the abdominal cavity, disappears.

e. Tunica vaginalis. The now isolated vaginal process or sac represents the tunica vaginalis of the testis; its visceral layer closely invests the testis whereas the parietal lines the scrotal sac.

f. Spermatic cord. The ductus deferens and spermatic vessels and nerves are carried down into the scrotum along with the testis and epididymis. They are surrounded by connective tissue and constitute the spermatic cord.

2. Ovaries. After their early migration they come to lie within the pelvis, where each rotates until it is placed in a transverse position.

G. The external genitalia.

1. Indifferent stage. Up to the beginning of the 8th week the external genitalia are identical in the two sexes.

a. Genital tubercle. This round eminence develops in the ventral body wall between the umbilical cord and the tail.

b. Urethral groove and folds. It is located on the caudal surface of the tubercle, and is separated from the anus by the primitive perineum. The margins of the groove are the urethral folds.

c. Phallus. This is visible by the end of the 7th week as a cylindrical prolongation ending distally as a rounded glans.

d. Labio-scrotal swellings. They occur on each side of the base of the phallus, from which they are separated by a groove.

2. **Transformation in the two sexes.** The fate of the parts just mentioned differs according to the sex, which cannot be recognized for sure until the end of the 10th week.

a. Male.

(1) Formation of the urethra. This is accomplished through transformation of the urethral groove into a hollow tube; the fused edges of the groove constitute the raphé.

(2) Migration of the scrotal swellings. These shift caudad and each becomes a half of the scrotum, separated from the other half by the raphé and the underlying scrotal septum.

(3) Elongation of the penis. It is accompanied by a continuation of the formation of the urethra, which finally reaches the glans.

(4) Corpora cavernosa. They arise as columns of mesenchyme within the shaft of the penis.

b. Female. The changes are less marked and take place much more gradually.

(1) Phallus. It lags in development and becomes the clitoris; its distal portion is the glans clitoridis.

(2) Urethral groove. This never reaches the glans, as in the male, but remains open as the vestibule.

(3) Urethral folds. They become the labia minora.

(4) Labio-scrotal swellings. They grow caudad and fuse in front of the anus as the posterior commisure, while their lateral portions are converted into the labia majora.

H. Anomalies. True hermaphroditism in man is very rare; false hermaphroditism, characterized by the presence of the genital glands of one sex with external genitalia and secondary sexual characteristics of the other, is much more frequent. When the lips of

the uro-genital sinus in males fail to fuse hypospadias result, a common feature in hermaphroditism of the female type.

THE SKELETAL SYSTEM

The supporting tissues (connective tissue, cartilage and bone) arise from mesenchyme, which consists of irregularly branched cells separated by uneven spaces filled with a fluid resembling lymph.

I. Connective Tissue

The mesenchyme cells become fibroblasts.

A. Origin of the fibers. The characteristic connective tissue fibers arise in the intercellular spaces rather than within the fibroblasts, as was formerly supposed.

1. **Argyrophil fibers.** These are the first to appear, remaining as such in the reticulum of certain organs (spleen, liver, lymph nodes).
2. **Collagenous fibers.** They arise through chemical transformation of argyrophil fibers which are aggregated into bundles.
3. **Elastic fibers.** Their development is not exactly known; they are laid down amongst the collagenous fibers.

B. Adipose tissue. Certain mesenchyme cells, called lipoblasts, give rise to fat cells. Fat droplets appear in their cytoplasm and coalesce into a large drop which pushes the nucleus to the periphery of the cell.

II. Cartilage

The mesenchymal cells which will give rise to cartilage lose their processes and are aggregated into a mass of polygonal cells, known as precartilage. The intercellular substance appearing between the cells becomes the ground substance or matrix of the cartilage and the cells are enclosed within lacunae.

III. Bone. Development of the Skeleton

The histogenesis of bone has already been described in the Histology (p. 18). From the standpoint of Embryology the skeleton is composed of two portions, the axial and appendicular skeleton, respectively.

A. Axial skeleton. This comprises the vertebral column and ribs, the sternum and the skull.

1. Vertebrae. The vertebral column and ribs originate from the sclerotomes of the somites (p. 109), which consist of spindle-shaped mesenchymal cells.

a. Blastemic stage. Each sclerotome differentiates into a caudal dense half, and a cranial less dense portion. The dense portion of each sclerotome mass later joins the looser cranial mass of the sclerotome right caudal to it, to form the substance of the vertebra.

(1) Formation of the body of the vertebra. The two sclerotomic portions enclose the notochord to form this part.

(2) Vertebral arch. From the dense half, dorsal extensions grow around the neural tube.

(3) Costal processes. These are ventro-lateral outgrowths.

(4) Intervertebral disks. They arise from mesenchyme derived from the dense portion of the sclerotome.

b. Chondrification. There are six centers: two in the vertebral body, one in each half of the vertebral arch, and one in each costal process. They enlarge and fuse into a solid cartilaginous vertebra.

c. Ossification. This occurs during the 10th week. There is a single center for the body of the vertebra and one in each half of its arch; the union of these parts is not completed until several years after birth.

2. Ribs. They arise from the costal processes; their original union with the vertebra is replaced by a joint which receives the head of the rib. The transverse process of the vertebra extends outward and articulates with the growing tubercle of the rib. There is a single center of ossification for each rib.

3. Sternum. Arises from paired sternal bars which unite the upper eight or nine cartilaginous thoracic ribs of each side. At an early period the two bars fuse together; this is followed by ossification.

4. The skull. Most of the bones of the skull arise from the chondrocranium; the flat bones of the vault and face (frontal, parietals, nasals, lacrimals, zygomatics and vomer) are purely membranous, whereas the occipital, sphenoid and temporals are mixed.

a. The chondrocranium. The chondrocranium is a continuous mass of cartilage extending from the occipital to the ethmoidal region and to a certain extent dorsally at the sides and behind.

(1) The periotic (auditory) capsules. They are formed by

cartilage which encloses the internal ear. They fuse with the chondrocranium.

(2) Ossification. Most cartilage bones of the skull develop from two or more formative centers. The ossification begins early in the third month. The occipital has four centers of ossification, the sphenoid five, the ethmoid four, and the temporal probably two.

b. Membrane bones of the skull. The frontal develops from two centers on each side of the midline, the parietals from one center each, the vomer from two, the nasal, lacrimal and zygomatic from one center each.

c. Branchial arch skeleton. This is formed by cartilage and membrane bones derived from the branchial arches.

(1) First (mandibular) arch. A cartilaginous bar (Meckel's cartilage) develops only in the mandibular process; the maxillary process has no cartilaginous skeleton but two membrane bones, the palatine and maxilla are developed in it, the former from one center, the maxilla from two or possibly more.

(a) Proximal portion of Meckel's cartilage. It extends into the tympanic cavity, where it forms two of the bones of the middle ear, the malleus (hammer) and incus (anvil).

(b) Distal portion. This is invested by membrane bone which forms the body and rami of the jaw; the membrane bones are paired, and fuse in the midline in a symphysis. The invested portion of Meckel's cartilage degenerates.

(2) Second (hyoid) arch. Its cartilage also enters the periotic capsule; this proximal segment gives rise to the stapes (stirrup) of the middle ear, the styloid process of the temporal, and the lesser horn of the hyoid bone. Between the latter and the styloid process failure of ossification produces the stylohyoid ligament.

(3) Third branchial arch. It produces the greater horns of the hyoid, while the plate (copula) connecting the two arches becomes the body of this bone.

(4) Fourth and fifth branchial arches. They differentiate into the cartilages of the larynx.

B. Appendicular skeleton. It is derived from the somatic mesenchyme which forms the core of the limb bud and becomes converted

into cartilage; ossification of the latter produces all the bones of the limbs, with the possible exception of the clavicle.

1. **Pectoral girdle and arm.**
   a. **The clavicle** is the first bone of the skeleton to ossify; it has two centers of ossification.
   b. **The scapula** has two chief centers, one for the body and spine, the other for the coracoid process, and several later epiphyseal centers.
   c. **The humerus,** radius and ulna all ossify from a single primary center in the diaphysis and an epiphyseal center at each end.
   d. **Carpals, metacarpals and phalanges.** Each carpal ossifies from a single center; the metacarpals and phalanges also have a single primary center and an additional epiphyseal center.
2. **Pelvic girdle and leg.**
   a. **The innominate** arises from three main centers of ossification, one for the ileum, one for the ischium, and another for the pubis. The three join in the acetabulum, which receives the head of the femur.
   b. **Femur, tibia and fibula.** Their development is similar to that of the corresponding bones of the arm. The patella is regarded as a sesamoid bone.
   c. **Tarsal, metatarsals and phalanges.** They develop as the corresponding bones of the hand.

THE MUSCULAR SYSTEM

The histogenesis of the three varieties of muscle has been already dealt with (pp. 21, 22, 24).

I. The Visceral Musculature

The muscle (smooth) associated with the hollow viscera arises from the splanchnic mesoderm (p. 109). The same layer originates the cardiac (striated) variety, which develops from the thickened epimyocardial lining on the outer surface of the cardiac tubes (p. 133).

II. The Skeletal Musculature

Most of the skeletal muscles originate from the myotomes. The differentiation of the skeletal muscles takes place rapidly, and at

about the 8th week they are already capable of correlated movements.

A. **Changes in the myotomes.**

1. **Migration,** wholly or in part, to more or less distant regions.
2. **Fusion** of portions of successive myotomes into a single muscle. With the loss of the segmental arrangement the original innervation of each portion of a myotome is retained throughout life.
3. **Splitting.** This may be longitudinal or tangential. In the first case the myotome gives rise to several subdivisions, in the second there is an increase in the number of layers. With the splitting there may be a change in the direction of the fibers.
4. **Degeneration of myotomes or parts of myotomes;** the degenerated portions may be changed into ligaments, fascias and aponeurosis.

B. **Muscles of the trunk.**

1. **The lateral and abdominal muscles** originate as ventral extensions of the myotomes; the somatic mesoderm gives rise only to the intermuscular connective tissue.
2. **The superficial portions** of a dorsal longitudinal column of fused myotomes on each side produce the various long muscles of the back, innervated by the dorsal rami of the spinal nerves.
3. **The intervertebral muscles** develop from the deeper, non-fused portions of the myotomes.

C. **Muscles of the neck.** The long muscles arise from the same longitudinal column producing the corresponding muscles of the trunk, and are also innervated by dorsal rami. Other muscles differentiate from ventral extensions of the cervical myotomes and from the branchial arches.

D. **Muscles of the head.** The head lacks definite somites but it is possible that the mesenchyme which gives rise to the eye muscles—supplied by somatic motor nerves (III, IV and VI)—is of myotomic origin. The other muscles of the head develop from the lateral mesoderm and retain their primitive branchial arch innervation.

1. **First (mandibular) arch.** Gives rise to the muscles of mastication (temporal, masseter, anterior belly of digastric, mylohyoid and pterygoids) and other muscles associated with the trigeminal (fifth) nerve (tensors of palatine velum and tympanum).
2. **Second (hyoid) arch.** Produces the muscles of expression (facial

muscles) and all other muscles supplied by the facial (seventh) nerve (stylo-hyoid, posterior belly of digastric, stapedius, platysma, occipito-frontal).

3. **Third arch.** This is the source of muscles supplied by the glosso-pharyngeal (ninth) nerve (stylo-pharyngeus and part of the pharyngeal constrictors).

4. **Fourth and fifth arches.** They give rise to part of the pharyngeal constrictors, certain muscles of the palate and the muscles of the larynx, all of which receive their supply from the vagus (tenth) nerve. The accessory (eleventh) nerve innervates the sterno-mastoid and trapezius, regarded as branchiomeric muscles.

E. Muscles of the limbs. The direct myotomic origin of these muscles in mammals is questionable even though there are indications of migration of mesenchyme cells from the edges of the cervical myotomes. The development of the upper limb muscles is more advanced than those of the lower limb, and the proximal muscles appear earlier than the distal in any case.

ECTODERMIC DERIVATIVES

THE INTEGUMENT AND ITS DERIVATIVES

Although it is included among the ectodermic derivatives the integument has a double origin.

I. The Skin

The superficial epithelium arises from ectoderm; the derma or corium from mesoderm.

A. Epidermis. In early embryos it is a single layer of cuboidal cells, but it soon becomes double-layered.

1. **Epitrichium (periderm).** This is the most superficial layer, composed of flattened cells. The term 'epitrichium' alludes to the fact that the layer is lifted off by the growing hairs. Failure of desquamation leads to ichthyosis, a condition which is frequently hereditary.

2. **Basal layer.** Made up of cuboidal cells which will give rise to the other layers of the epidermis. Stratification occurs after the 4th month.

3. Vernix caseosa. This is a mixture of desquamated epidermal cells, lanugo hairs and sebaceous secretion which covers the fetal skin and prevents its maceration by the amniotic fluid.

B. Derma. In most vertebrates it arises from the dermatomes of the somites (p. 109), but it has been claimed that dermatomes are absent in mammalian embryos. The derma, therefore, probably arises from mesenchyme.

II. The Hair

The earliest hairs begin to appear at the end of the second month on the eyebrows, upper lip and chin; later (4th month) the body hair develops. The latter is at first fine and silky, and is known as lanugo.

A. Development. A hair follicle begins as a cluster of basal layer cells in the epidermis.

1. Elongation. The cluster becomes elongated and gradually sinks into the underlying derma.

2. Differentiation. The base of the hair primordium enlarges into the bulb, which fits as a cap on the surface of the mesenchyme mass which will become the papilla.

3. Structure. The follicle at this stage consists of two layers:

a. An outer layer of columnar cells continuous with the basal layer of the epidermis; they give rise to the outer sheath.

b. A core of polyhedral cells, which produces the substance of the hair.

c. Connective tissue sheath. This arises from mesenchyme.

4. Growth of the hair. The hair is a proliferation from the basal epidermal cells next to the papilla. They produce an axial core which becomes the inner sheath and shaft, respectively.

III. The Sebaceous Glands

Most sebaceous glands develop in connection with the hair follicles. They arise as solid epidermal buds which become lobulated.

IV. The Sweat Glands

Some develop in connection with hair follicles, from which they separate later, but most appear independently as solid downgrowths from the epidermis. The simple, cylindrical downgrowths coil and acquire lumina. The walls of the tubules consist of:

A. An inner layer of cuboidal cells, which become the glandular elements.
B. An outer layer, whose cells become transformed into myo-epithelial, contractile elements (p. 48).

V. The Mammary Glands

They are usually regarded as modified sweat glands and appear early in the two sexes as longitudinal ectodermal thickenings which extend on each side between the bases of the limb buds. Each ridge is called the milk line.
A. Disappearance of the milk line. In man the milk line is best seen in the pectoral region; the more caudal portion soon disappears. If persistent it gives rise to accessory mammary glands.
B. Development of the glands. Each gland begins as a downgrowth from the milk line in the region of the future breast. The primordium gradually grows into 15-20 cords (primary milk ducts) which branch in the derma and give rise to acini.
C. Development of the nipple. Where the milk ducts open the epidermis is raised to form the nipple; this may not happen until after birth.

THE NERVOUS SYSTEM

The central nervous system develops from the neural plate, an ectodermic band along the mid-dorsal line of the embryo (p. 108).

I. The Central Nervous System

A. Histogenesis. The neural tube gives rise to all the nervous tissues except the cerebrospinal and sympathetic ganglia, and the olfactory neurones (p. 95). The primitive cells of the tube differentiate into two kinds of elements, namely, the nerve cells and the supporting cells.

1. Early differentiation of the neural tube. Its wall shows at first several indistinct layers; later it becomes separated into three distinct zones:

a. Inner (ependymal) zone, near the lumen of the tube from which it is separated by a thin internal limiting membrane; its cells send processes toward the periphery. It constitutes most of the roof and floor of the neural canal (roof and floor plates).
b. Middle (mantle) zone, consisting of many, closely packed

cells; it becomes the gray matter, and contributes to the marked thickening of the lateral walls of the neural tube.

c. Marginal zone, largely non-nucleated and gradually invaded by the axons of the cells of the preceding zone; it becomes the white matter. Externally it is bounded by the outer limiting membrane.

d. Sulcus limitans. A groove on the inner surface of each lateral wall subdivides the latter into a dorsal alar plate (sensory) and a ventral basal plate (motor).

2. Differentiation of the neuroblasts. The neuroblasts are the embryonic nerve cells which become the neurones of the adult. They arise from germinal cells which occur in the ependymal zone and divide by mitosis.

a. Development of efferent neurones. The neuroblasts become pear-shaped and from the narrow end of the cell a slender axon grows. Later they acquire neurofibrils and develop dendritic processes. Many axons leave the spinal cord as ventral roots.

b. Development of the ganglia. They arise from the:

(1) Neural (ganglion) crest, which is a longitudinal ridge of cells on each side, where the ectoderm joins the wall of the neural groove.

(2) Migration of the crest. After closure of the neural tube (p. 108) the neural crests separate into right and left halves which occupy a position between the tube and the dorsal portions of the myotomes.

(3) Segmentation into spinal ganglia. The continuous neural crest bands caudal to the otocysts soon show swellings which become spinal ganglia. The portions of the crest between the ganglionic swellings disappear.

(4) Formation of the cranial ganglia. These also develop from the crest but are not segmentally arranged. Certain cranial ganglia receive contributions from ectodermal thickenings called placodes.

(5) Formation of sympathetic ganglia. They are believed by some to originate from the neural crest.

c. Development of afferent neurones. The cells of the cerebrospinal ganglia differentiate into ganglion cells (afferent neurones) and supporting cells.

(1) Bipolar stage. The ganglionic neuroblasts become spindle-shaped, and are transformed into bipolar neurones (p. 24) through growth of a process at each end. They remain in this condition in the auditory ganglia (p. 31).

(2) Dorsal roots. They are formed by processes (axons) directed toward the neural tube. They enter the latter and bifurcate into an ascending and a descending process coursing in the dorsal region of the tube. Collaterals from the processes establish connection with the neurones of the mantle layer.

(3) Peripheral processes. These pass outward and join the axons of the efferent neurones of the cord coursing into the ventral roots; the common bundles thus constituted are the trunks of the spinal nerves.

(4) Transformation into monopolar neurones. While some neuroblasts remain in the bipolar stage most others are changed into monopolar neurones chiefly by fusion, for a variable distance from the cell body, of the two primary processes into a common stem.

3. Differentiation of the supporting elements. These arise from spongioblasts, which originate from the undifferentiated cells of the neural plate tissue.

a. In the neural tube. For some time the spongioblasts are elongated and radially arranged within the tube, with their nuclei placed close to the lumen; the inner end of the cell touches the internal limiting membrane, while the outer reaches the periphery of the tube.

(1) Ependymal cells. These are spongioblasts which retain their primitive shape and position.

(2) Neuroglia cells. Many of the elongated spongioblasts lose their connections with the lumen of the neural tube, and some of them also lose their peripheral portion, to become neuroglia cells (astroglia and oligodendroglia, p. 33).

b. In the ganglia. The supporting cells become capsule cells, satellite cells (p. 31), and sheath cells; the latter migrate peripherally along with the growing axons and envelop them as neurilemma or cells of Schwann (p. 27).

B. Morphogenesis. The formation of the neural tube and the subdivision of its anterior, expanded end into the three primary brain

vesicles have already been described (p. 108). The rest of the tube is the spinal cord.

1. The spinal cord. The typical three zones described previously are clearly seen by the 5th week.

a. Shape. At first cylindrical it becomes enlarged at the level of the two nerve plexuses that supply the limbs (cervical and lumbar enlargements, respectively).

b. Decrease in growth. After the 3rd month the vertebral column grows faster than the spinal cord. Since the latter is anchored to the brain the caudal displacement of the vertebrae causes an elongation of the roots of the lumbo-sacral nerves, which together constitute the cauda equina.

c. Filum terminale. Since the posterior end of the neural tube retains its terminal connections during the period of unequal growth the caudal portion of the tube becomes this slender, fibrous strand which occupies the axis of the cauda equina.

d. Formation of the central canal. The neural canal is at first quite large and roughly diamond-shaped in cross section. Later the lateral walls fuse dorsally (i.e. above the sulcus limitans); in this way the dorsal portion of the canal is obliterated and the persisting ventral portion becomes the definitive central canal.

e. Differentiation of the walls. The thickening of the lateral walls of the early spinal cord dominates the final arrangement of the gray and white matter and is largely responsible for the disappearance of the roof plate and reduction in size of the floor plate.

(1) Formation of the dorsal median septum. This arises largely from the fused ependymal layers during obliteration of the dorsal portion of the neural canal.

(2) Formation of the ventral median fissure. The floor plate lags in development and since it is interposed between the rapidly thickening ventral portions of the lateral walls these fail to meet, giving rise to the fissure.

f. Anomalies. The spinal cord may be absent, or the neural tube may have failed to close; this condition often accompanies cleft spine which is really a defect of the vertebral column. A sac may protrude through the cleft and may be formed by the cord

only (myelocele) or by the cord and its meninges (meningomyelocele).

2. The brain. Of the three primary vesicles (p. 108) the first and last are subdivided into two secondary vesicles each: the telencephalon and diencephalon, in the case of the fore-brain (prosencephalon), and the metencephalon and myelencephalon, in the case of the hind-brain (rhombencephalon).

a. Cavities. With the subdivision of the primary vesicles the number of cavities is increased to four.

(1) Lateral ventricles. The cavity of the telencephalon extends into the paired hemispheres as the lateral (first and second) ventricles.

(2) Third ventricle. This is the cavity of the median portion of the telencephalon plus the cavity of the diencephalon.

(3) Fourth ventricle. It includes the merged lumina of the metencephalon and myelencephalon; it is continuous caudally with the central canal of the spinal cord.

(4) Cerebral aqueduct (of Sylvius). The mid-brain (mesencephalon) remains undivided; its primitive cavity becomes this narrow canal connecting the third and fourth ventricles.

b. Myelencephalon (medulla oblongata). It is the transition between the spinal cord and the brain. Its walls undergo certain differentiations.

(1) Roof-plate. This, instead of disappearing, as in the spinal cord, becomes the thin ependymal roof of the 4th ventricle.

(2) Chorioid plexus. Blood vessels grow into the layer of mesenchyme (tela chorioidea) which covers the outer surface of the ependymal roof and upon invagination of the latter they form this plexus.

(3) Lateral walls. The sulcus limitans persists, separating each wall into an alar and a basal plate.

(4) Floor plate. It persists and its ependymal cells elongate as the ventral wall of the myelencephalon thickens; the processes of the ependymal cells extend from the floor of the fourth ventricle to the ventral surface as the raphé.

(5) Nuclei of the alar plate. Neuroblasts arrange themselves into the terminal (receptive) nuclei of nerves V, VII, VIII, IX and X.

(6) Nuclei of the basal plate. Efferent neuroblasts form the motor nuclei of origin of nerves V, VI, VII, IX, X, XI, and XII.

c. **Metencephalon.** In general structure is similar to the preceding but it is the site of a marked embryonic flexure, and it also develops two specialized parts, the pons and cerebellum, respectively.

(1) Pontine flexure. This, although temporary, is highly characteristic of the embryo. Its convexity is ventrally directed. It disappears completely during fetal life.

(2) Roof-plate. Part of it is transformed into a thin plate of white matter both in front and behind the cerebellum, known as the anterior and posterior medullary velum, respectively; the other part merges with the cerebellum.

(3) Lateral walls. The still present sulcus limitans divides them into alar and basal plates. In the latter develop the motor nuclei of nerves V, VI, and VII, along with the reticular formation, present also in the myelencephalon. The alar plates contribute to the formation of the:

(4) Cerebellum. The plates assume a transverse position as the pontine flexure develops. Paired swellings near the midline foreshadow the vermis, while the lateral portions become the cerebellar hemispheres. The latter connect with the pons by means of the brachium pontis (middle cerebellar peduncle).

(5) Pons. The pons develops as a thickening of the anterior wall of the pontine flexure.

(6) Floor plate. This forms the portion of the raphé within this region, where it is said to end.

d. **Mesencephalon.** This is the least-modified portion of the primitive brain tube.

(1) Roof plate. It becomes very narrow and finally disappears.

(2) Alar plates. They develop into the lamina that bears the corpora quadrigemina (superior and inferior colliculi), composed of stratified layers of neuroblasts.

(3) Basal plates. Their efferent neuroblasts form the motor nuclei of nerves III and IV. The tegmentum is to be regarded as an anterior extension of the reticular formation of the mete- and myelencephalon.

(4) Floor plate. It is absent in the mesencephalon and anterior to it.

(5) Cerebral peduncles. They occur on each side of the midline in the floor of the mesencephalon, and are composed of nerve fibers from the fore-brain and of sensory tracts coursing in the opposite direction.

e. Diencephalon. It lacks floor and basal plates, and nerves do not arise from it. It is connected ventrally with the hypophysis (pituitary body). Its cavity is the third ventricle.

(1) Roof plate. It becomes a thin plate in which the chorioid plexus of the third ventricle develops.

(2) Alar plates. Each of these is subdivided into three main regions:

(a) Epithalamus, at the junction of the caudal portion of the roof plate with the alar plate. The pineal gland (epiphysis cerebri) arises from this region.

(b) Thalamus. This is a marked swelling on the lateral wall; the two thalami may join each other in the midline through the massa intermedia. Ventrally is the:

(c) Hypothalamus, containing the infundibulum, tuber cinereum, and mammillary bodies.

(3) The hypophysis. This important endocrine has a double origin.

(a) Anterior lobe. It develops from an invagination of the roof of the stomodaeum just in front of the pharyngeal membrane (Rathke's pouch). The invaginated ectodermic sac sinks beneath the epithelium, and becomes a hollow vesicle whose cavity is the residual lumen of the adult gland (p. 90).

(b) Posterior lobe (pars nervosa). This is the enlarged tip of the infundibular process, which grows as an invagination of the floor of the diencephalon and meets the hollow vesicle arising from Rathke's pouch.

(4) Optic stalks. They are connected with each side of the diencephalon (p. 166).

f. Telencephalon. It becomes the most specialized and complex region of the mammalian brain. It consists of a median portion, continuous posteriorly with the diencephalon and containing

the cephalic part of the third ventricle, and two lateral outpocketings, the cerebral hemispheres.

(1) Roof plate. It gives rise to the chorioid plexus.

(2) Alar plates. They produce practically the whole cerebral hemispheres.

(3) Cerebral hemispheres. They arise between the 5th and 6th week, and grow beyond the original rostral end of the neural tube, the wall of which is the lamina terminalis.

(a) Lateral ventricles. These are the cavities of the hemispheres; they communicate with the third ventricle through the paired interventricular foramina (of Monro).

(b) Corpus striatum. This is a thickening of the floor of the hemisphere. The groove separating it from the thalamus disappears and the two portions merge into a continuous mass.

(c) Internal capsule. Nerve fibers coursing between the striate body and the thalamus are gathered into a V-shaped lamina, open laterally. This is the internal capsule, which partly subdivides the corpus striatum into secondary masses (caudate and lenticular nuclei).

(d) Rhinencephalon. It is represented by the olfactory lobes which arise as swellings of the ventral surfaces of the hemispheres. The rostral or anterior part of each develops into the olfactory bulb and tract. Connected with the olfactory apparatus there is also a portion of the brain cortex (hippocampal system).

II. The Peripheral Nervous System

The formation and early differentiations of the neural crests have already been considered (pp. 108, 156).

A. The spinal nerves. Each nerve is attached to the cord by two roots: dorsal and ventral.

1. Dorsal root. It has a spinal ganglion associated with it. The neuroblasts send their axons into the marginal zone of the cord as dorsal root fibers; their peripheral processes join the ventral root fibers.

2. Ventral root. This carries efferent fibers (axons of cells within the cord).

3. **Nerve trunks.** The mixed nerve trunks give off:

   a. **A dorsal ramus,** supplying the dorsal skin and musculature; it continues as:

   b. **The ventral ramus** which in turn sends a:

   c. **Ramus communicans,** to the sympathetic; the ramus communicans carries efferent fibers (preganglionics).

   d. **The lateral and ventral terminal rami** arise through division of the ventral ramus.

4. **Plexuses.** They are produced through anastomoses between the spinal nerves. The brachial and lumbo-sacral plexuses arise in this manner.

B. **The cranial nerves.** The cranial nerves are not segmentally arranged. There are twelve pairs of which three are purely (special) sensory, four are purely (somatic) motor while the other five are mixed (except the spinal accessory, purely motor in the adult but intimately associated with the vagus).

1. **Special sensory:**

   a. **Olfactory (I).** It has no ganglion. For its termination see p. 96.

   b. **Optic (II).** Consists of axons of neurones in the retina (p. 99).

   c. **Auditory (VIII).** Axons growing from the auditory ganglia (vestibular and cochlear).

2. **Somatic motor:**

   a. **Oculomotor (III).** Nucleus of origin in the basal plate of the mesencephalon.

   b. **Trochlear (IV).** Nucleus of origin as in the preceding, but more caudally placed.

   c. **Abducens (VI).** Nucleus of origin in the pontine region of the metencephalon.

   d. **Hypoglossal (XII).** Nucleus of origin in the basal plate of the myelencephalon; associated in embryonic life with rudimentary dorsal ganglia (of Froriep) which later disappear.

3. **Visceral sensory and motor:**

   a. **Trigeminal (V).** Chiefly sensory; its main ganglion (semilunar or Gasserian ganglion) gives off three branches: ophthalmic, maxillary and mandibular. The motor nucleus sends fibers to the muscles of mastication.

b. Facial (VII). Chiefly motor; its sensory fibers are prolongations of neurones in the geniculate ganglion and end in the sensory organs of the tongue.

c. Glossopharyngeal (IX). Chiefly sensory; its motor fibers arise from the nucleus ambiguus, which it shares with the vagus. They innervate some of the pharyngeal muscles (p. 153). The sensory fibers are the peripheral processes of the superior and petrosal ganglia.

d. Vagus (X) and spinal accessory (XI). They occur as a complex.

(1) The motor fibers arise from nuclei in the spinal cord (spinal portion of accessory) and myelencephalon (bulbar portion of accessory; motor portion of the vagus). The accessory fibers soon separate from the vagus, which supplies motor fibers for the pharynx and larynx.

(2) The sensory fibers are processes of neurones residing in the jugular and nodose ganglia, respectively.

C. The sympathetic nervous system. Its origin is still a matter of discussion. The ganglia of the trunk develop before those of the head and neck region.

1. Formation of the sympathetic chains. The sympathetic primordia are first continuous neuroblastic bands; later the neuroblasts concentrate into segmentally arranged ganglia, connected by a longitudinal nerve cord (sympathetic trunk).

2. The collateral ganglia. The collateral ganglia (ganglia of the prevertebral plexuses) develop later.

3. Cranial sympathetic ganglia. The ciliary, spheno-palatine, and otic ganglia (parasympathetic) are not segmental and are derived mainly from the primitive semilunar (Gasserian) ganglion.

4. Chromaffin bodies. These, arising from cells in the primitive sympathetic ganglia which give the chromaffin reaction (p. 94), occur in close proximity to the ganglia (paraganglia) and in the abdominal sympathetic plexus. They gradually degenerate after birth, except the largest which is the:

5. Suprarenal gland. It has a double origin:

a. Medulla. Its chromaffin cells (ectodermic) are derived from the coeliac plexus. They arise as masses of cells which invade the median side of the primordium of the:

b. Cortex. The cortex is of mesodermic origin and arises as proliferations of the peritoneal lining, on each side of the root of the mesentery. The early suprarenals are quite large and project from the dorsal coelomic wall, between the mesonephros and mesentery.

6. Carotid body (glomus caroticum). Although usually included among the paraganglia, its paraganglionic nature is doubtful since it has been shown to be a chemoreceptor (p. 30).

THE SENSE ORGANS

Only the specialized sense organs will be considered here.

I. The Organ of Taste

The taste buds arise as local thickenings of the tongue epithelium as well as the epithelium of the oral mucosa, pharynx and epiglottis. The cells of the thickening become the characteristic elements of the bud (p. 95). In late fetal life many of the taste buds degenerate and the adult distribution is attained.

II. The Nose

The early development of the nose has been considered in the section dealing with the formation of the face (p. 112).

A. Formation of the primitive choanae. The epithelial plates which separate the nasal fossae from the mouth cavity rupture caudally to produce these internal nasal openings. The nasal fossae now have outer (nostrils) and inner openings (choanae).

B. Formation of the lip and premaxillary palate. The front part of each epithelial plate is invaded by mesoderm, and becomes these parts.

C. The nasal septum. This arises from the medial fronto-nasal process (p. 112), which becomes narrower between the nasal fossae.

D. Separation of the nasal passages from the mouth cavity. It takes place after fusion of the palatine processes in the midline (p. 123). Fusion of the ventral border of the septum with the palate completes the separation of the nasal passages.

E. The permanent choanae. Their formation is finally accomplished by the fusion mentioned above. The permanent nasal passages con-

sist, therefore, of the nasal fossae plus a portion of the primitive mouth cavity.

F. Vomero-nasal organs (of Jacobson). They are rudimentary epithelial sacs which open toward the front of the nasal septum. They usually degenerate in late fetal stages.

G. The conchae. They arise as folds on the lateral and medial walls of the nasal fossae; first cartilage, then bone develops in them.

H. The sinuses. They arise through absorption of bone. The spaces thus formed are soon lined by epithelium which evaginates from the nasal passages.

III. The Eye

Its development is complex. The sensory portion (retina) arises from the brain as optic vesicles, while the lens is an invagination of the ectoderm in front of each vesicle.

A. The optic vesicles. These are outpocketings of the fore-brain to which they are attached by narrower optic stalks.

1. The optic cups. They arise through invagination of the lateral hemisphere of the vesicle into the mesial hemisphere. A double-walled cup is thus produced, connected with the diencephalon by the optic stalk.

a. The chorioid fissure. The invaginated portion of the vesicle is notched ventrally, the notch extending along the ventral surface of the optic stalk as a groove (chorioid fissure), through which the central artery of the retina reaches the optic cup.

(1) Closure of the fissure. It becomes a tube through approximation and fusion of its edges. Incomplete closure supposedly gives rise to absence of a sector of the iris, ciliary body or chorioid; this is known as coloboma.

(2) Obliteration of the optic stalk. This takes place upon growth of axons from the retina. The axons fill the lumen of the stalk on their way to the brain and the stalk is transformed into the optic nerve.

b. Pigment layer. The outer, thinner layer of the optic cup becomes this portion of the adult retina. Pigment appears very early.

c. Nervous layer. The internal, thicker layer of the cup becomes this retinal portion.

(1) Pars caeca. This is the zone bordering the rim, which

later is subdivided into the pars ciliaris and pars iridica, respectively (pp. 97, 98).

(2) Pars optica (visualis). The more centrally located portion, separated from the former by the ora serrata. In it develop the rods and cones and the other layers of the adult retina (p. 98).

B. The lens. The ectoderm in front of the optic vesicle thickens to form the lens placode, which is soon changed into a vesicle.

1. **Position.** After invagination of the placode has ended the lens vesicle occupies the concavity of the optic cup.

2. **Differentiation of the walls.** From its early formation the lateral wall of the vesicle is thinner than the medial wall.

a. **Lens epithelium.** The cells of the lateral wall remain as low columnar elements and form this part of the lens.

b. **Lens fibers.** The cells of the medial wall become much elongated, their nuclei degenerate and they become the transparent long prisms or fibers.

c. **Disappearance of the lens cavity.** This is gradually obliterated when the rapidly elongating fibers come to be in contact with the posterior surface of the lens epithelium.

3. **Capsule.** It is apparently formed by the cells of the lens vesicle, but it lacks a definite structure.

C. The vitreous body. Fills the space between the lens and retina; it is produced by the latter, and is secondarily invaded by mesenchyme, some of which enters with the central artery.

1. **The hyaloid artery.** This is the branch of the central artery that crosses the developing vitreous body and spreads over the posterior surface of the lens. It degenerates, leaving the hyaloid canal (p. 100).

2. **Pupillary membrane.** This contains small vessels supplying the rest of the lens; they are derived from the peripheral rim of the chorioid.

D. The fibrous and vascular coats. They arise from mesenchyme which forms a double layer around the developing eye. The outer layer gives rise to the sclera and cornea, while the inner produces the iris, ciliary body and choroid. The anterior chamber arises as the result of degeneration of the mesenchyme between the lens and the surface ectoderm. Its continuous peripheral extension separates the iris from the cornea.

IV. The Ear

The formation of the external auditory meatus and the tympanic cavity has been already indicated (p. 124), as well as the origin of the ossicles of the middle ear (p. 150). Only the internal ear will be considered here. Its epithelial lining is of ectodermic origin.

A. The auditory placode. This is an area of thickened ectoderm located on each side of the hind-brain. The placodes appear very early, when a few somites are present in the embryo.

B. The otocyst, or auditory vesicle results from invagination of the placode. It loses all connection with the outside, but near the point where the otocyst joined the ectoderm there appears the:

1. **Endolymphatic duct,** which is a tubular outpocketing ending blindly distally; the blind end is the endolymphatic sac.
2. **Division into regions.** The otocyst elongates dorso-ventrally; its narrow ventral part becomes the:
    a. **Cochlear duct,** which will soon coil to form the cochlea.
    b. **Vestibular portion.** This is the more expanded, dorsal portion of the otocyst.
3. **Subdivision of the vestibular portion.** This will produce dorsally the:
    a. **Semicircular canals.** The anterior and posterior arise from a single pouch at the dorsal border while the lateral begins as a horizontal outpocketing placed a little more ventrally.
    b. **Formation of the ampullae.** The anterior and posterior semicircular canals have a common opening dorsally into the vestibule, but their opposite ends and the rostral end of the lateral canal are dilated into the ampullae (p. 102).
    c. **Utriculus and sacculus.** They develop from the more ventral part of the vestibular portion through the formation of a constriction. The semicircular canals are attached to the utriculus, while the cochlea is connected with the sacculus.
    d. **Further development.** The general shape of the inner ear of the adult is attained during the 3rd month. The utriculus and sacculus become separated from each other, but they keep their connection with the endolymphatic duct.

C. The bony labyrinth.

1. **Production of cartilage.** The mesenchyme surrounding the de-

veloping otocyst (membranous labyrinth) produces cartilage which completely encloses the labyrinth.

2. **Formation of the perilymphatic space.** Later on the cartilage next to the labyrinth undergoes regression and the space thus formed becomes the perilymphatic space.

3. **Ossification.** The bony labyrinth is produced during the 5th month by replacement of the cartilage capsule by bone. The modiolus of the cochlea develops directly from mesenchyme as a membrane bone.

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